VOL. 32 MAY 1956 NO. 5

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles by

JAMES L. WHITTENBERGER

THOMAS P. ALMY,
DAVID M. ROSEMAN
and WARREN S. BRAVEMAN

IAGO GALDSTON

MANAGEMENT OF PANCREATITIS
ACUTE AND CHRONIC

Transcription of a Panel Meeting on Therapeutics

CHARLES F. WILKINSON, Jr. J. WILLIAM HINTON
MICHAEL LAKE MILTON R. PORTER

NEW YORK PATHOLOGICAL SOCIETY

AUTHORITATIVE SOURCES CONTINUE TO CONFIRM THE WIDE MARGIN OF SAFETY OF—

GITALIGIN®

(WHITE'S BRAND OF AMORPHOUS GITALIN)

A digitalis preparation of choice for routine management of congestive heart failure, Gitaligin's wide therapeutic range permits rapid digitalization and successful maintenance with a minimum of toxic side reactions—even in refractory cases where other glycosides have failed.

•

Simple dosage equivalent: 0.5 mg. (1 tablet) of Gitaligin is approximately equivalent to 0.1 Gm. (1½ gr.) digitalis leaf, 0.5 mg. digoxin or 0.1 mg. digitoxin.

Gitaligin is supplied in 0.5 mg. tablets, deep scored for accuracy and flexibility of dosage—in bottles of 30 and 100.

WHITE LABORATORIES, INC.
Kenilworth, N. J.

"The clinical application of the wide difference between toxic and therapeutic dose in gitalin [Gitaligin] is an important advance in the pharmacology of cardiac glycosides."

Dunnicoff, E. P.; Griffith, O. C.; Thorner, M. C., and Walker, J.: Annals of Int. M. 39:1189 (Dec.) 1953.

---

5 out of 9 patients "did not manifest toxic symptoms even after 6 to 24 weeks at dosage levels 3 to 6 times their minimal maintenance requirement."

Weiss, A., and Steigmann, F.: Amer. J. Med. Sc. 227:188 (Feb.) 1954.

"...in the refractory cases of heart failure where desirable digitalis effect cannot be maintained without toxicity (the therapeutic range having dwindled to nothing as it tends to do in advanced heart disease), gitalin [Gitaligin] with its wider therapeutic range may still be effective when other preparations have been found wanting."

Marriott, H. J. L.: Editorial, Annals of Int. M. 40:820 (April) 1954.

"Instead of requiring two-thirds of the toxic dose before attaining a therapeutic effect, the usual patient will respond when approximately one-third of the total toxic dose is administered."

Batterman, R. C.; DeGraff, A. C., and Rose, O. A.: Circulation 5:201 (Feb.) 1952.

STABILIZE

the up and down patient

Serpasil
tranquilizer

Ritalin
psychomotor stimulant

Serpatilin
emotional stabilizer

To induce emotional equilibrium in those who swing from anxiety to depression, Serpatilin combines the relaxing, tranquilizing action of Serpasil with the mild mood-lifting effect of the new cortical stimulant, Ritalin. In recent months, numerous clinical studies have indicated the value of combining these agents for the treatment of various disorders marked by tension, nervousness, anxiety, apathy, irritability and depression. Arnoff,[1] in a study of 51 patients, found the combination of definite value in a variety of complaints, noting no effect on blood pressure or heart rate. Lazarte and Petersen[2] also found Serpatilin effective in counteracting the side effects of reserpine and chlorpromazine. They reported: "The stimulating effect of Ritalin seemed complementary to the action of reserpine . . . in that it brought forth a better quality of increased psychomotor activity."

1. Arnoff, B.: Personal communication. 2. Lazarte, J. A., and Petersen, M. C.: Personal communication.

Serpatilin Tablets, 0.1 mg./10 mg., each containing 0.1 mg. Serpasil® (reserpine CIBA) and 10 mg. Ritalin® hydrochloride (methyl-phenidylacetate hydrochloride CIBA).

Dosage: 1 tablet b.i.d. or t.i.d., adjusted to the individual.

Serpatilin T.M.

(reserpine and methyl-phenidylacetate hydrochloride CIBA)

CIBA
SUMMIT, N. J.

new

Against Pathogen & Pain

in urinary tract infections

Azo Gantrisin combines the single, soluble sulfonamide, Gantrisin, with a time-tested urinary analgesic - in a single tablet.

Prompt relief of pain and other discomfort is provided together with the wide-spectrum antibacterial effectiveness of Gantrisin which achieves both high urinary and plasma levels so important in both ascending and descending urinary tract infections.

Each Azo Gantrisin tablet contains 0.5 Gm Gantrisin 'Roche' plus 50 mg phenylazo-diamino-pyridine HCl. Gantrisin® - brand of sulfisoxazole

ROCHE

Original Research in Medicine and Chemistry

The Bulletin of The New York Academy of Medicine, Vol. 32, No. 5, May, 1956. Published Monthly by The New York Academy of Medicine, 2 East 103 Street, New York 29, N. Y. Entered as second-class matter February 3, 1928, at the Post Office at New York, N. Y., under the Act of August 24, 1912. Annual subscription United States and Canada $6.50. All other countries $7.50. Single copies 75c.

a "judicious combination..."

for antiarthritic therapy

SALCORT*

That cortisone and the salicylates have a complementary action has been well established.[1-5] In rheumatic conditions, functional improvement and a sense of feeling well are noted early. No withdrawal reactions have been reported.

One clinician states: "By a judicious combination of the two agents . . . it has been possible to bring about a much more favorable reaction in arthritis than with either alone. Salicylate potentiates the greatly reduced amount of cortisone present so that its full effect is brought out without evoking undesirable side reactions."[1]

INDICATIONS:

Rheumatoid arthritis . . . Rheumatoid spondylitis . . . Rheumatic fever . . . Bursitis . . . Still's disease . . . Neuromuscular affections

EACH TABLET CONTAINS:

Cortisone acetate	2.5 mg.
Sodium salicylate	0.3 Gm.
Aluminum hydroxide gel, dried	0.12 Gm.
Calcium ascorbate (equivalent to 50 mg. ascorbic acid)	60 mg.
Calcium carbonate	60 mg.

* U.S. Pat. 2,691,662

1. Busse, E.A.: Treatment of Rheumatoid Arthritis by a Combination of Cortisone and Salicylates. Clinical Med. 11:1105 (Nov., 1955).
2. Roskam, J., VanCawenberge, H.: Abst. in J.A.M.A., 151:248 (1953).
3. Coventry, M.D.: Proc. Staff Meet., Mayo Clinic, 29:60 (1954).
4. Holt, K.S., et al.: Lancet, 2:1144 (1954).
5. Spies, T.D., et al.: J.A.M.A., 159:645 (Oct. 15, 1955).

BRISTOL, TENNESSEE
NEW YORK
KANSAS CITY
SAN FRANCISCO

The S. E. Massengill company

MERATRAN Profile **DELAYED POSTPARTUM DEPRESSION**

Delayed Postpartum Depression

Sex: Female Age: 28 Occupation: Housewife
Chief Complaint: fatigue

Symptoms: crying spells, fainting spells, marked premenstrual depression

Observations: two normal births after period of "infertility" sudden change in household routine too much to cope with.

Treatment: Amphetamine and phenobarbital failed.
Meratran given 1 mg. t.i.d. - July 1954
Treatment stopped, symptoms returned
Meratran 1 mg. t.i.d. resumed May 1955.

Response: depression relieved.

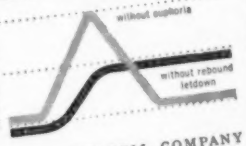
Results: Able to carry on her household duties husband said everything was going very smoothly.

One more case in point for

Meratran

in functional fatigue and mild depression

Meratran restores your emotionally tired and depressed patients to their usual level of alertness, interest and productivity



In doses individualized to the patient, Meratran produces a subtle, comfortable onset of action, prolonged effectiveness, and well-being without jitters or apprehension. There is no significant effect on blood pressure or respiration, little or no insomnia, no effect on normal appetite, no tolerance or drug habituation; wide range of safety.

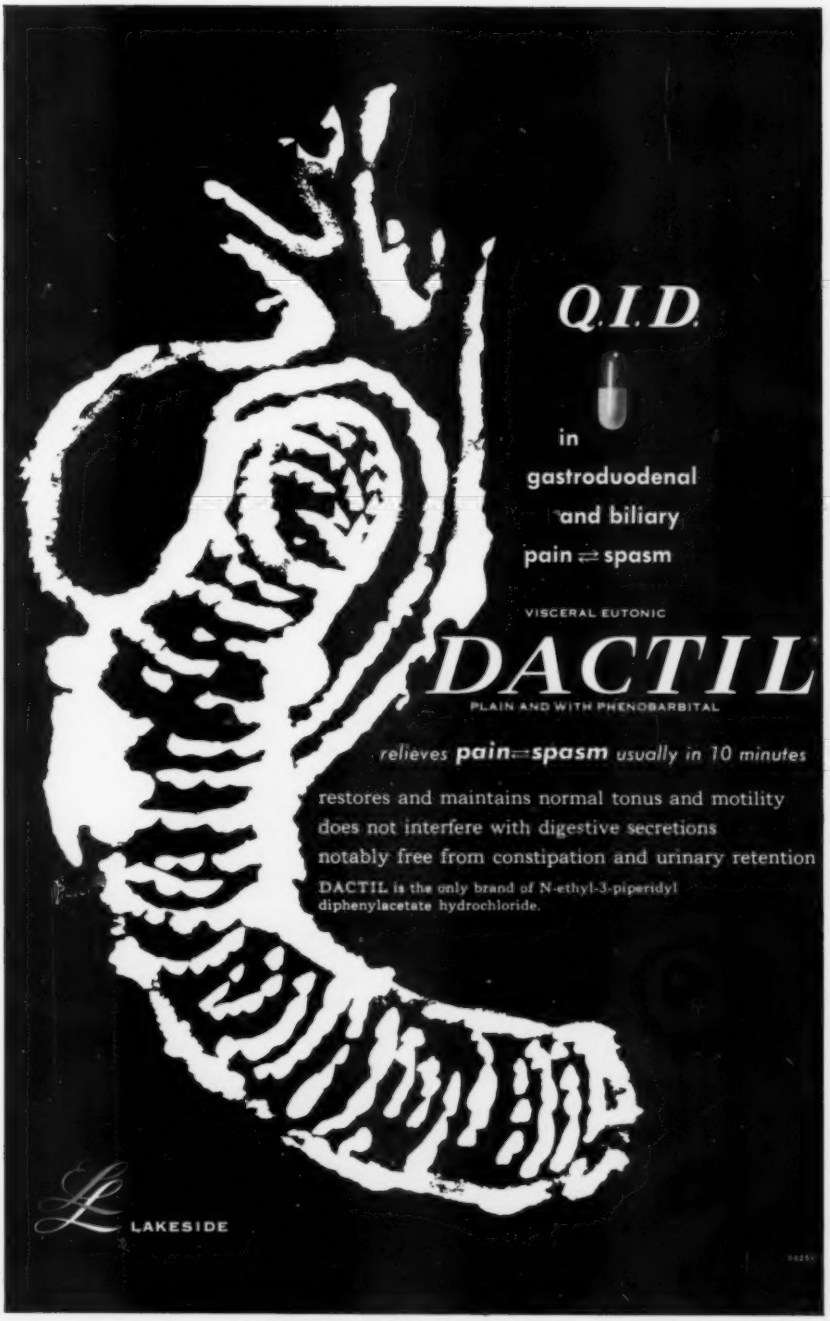
Dose: 6 mg. daily, adjusted downward to patient need.

THE WILLIAM S. MERRELL COMPANY
New York • CINCINNATI • St. Thomas, Ontario

Merrell

Another exclusive product of original Merrell research

*Case history from the actual files of an eminent physician; photo professionally posed.


Q.I.D.
in
gastroduodenal
and biliary
pain ⇄ spasm
VISCERAL EUTONIC
DACTIL
PLAIN AND WITH PHENOBARBITAL
relieves pain⇄spasm usually in 10 minutes
restores and maintains normal tonus and motility
does not interfere with digestive secretions
notably free from constipation and urinary retention
DACTIL is the only brand of N-ethyl-3-piperidyl diphenylacetate hydrochloride.
LAKESIDE

for results you can trust...

patients' reports you can rely on...

color calibrated

CLINITEST®

BRAND

the urine-sugar test with the Laboratory-Controlled color scale

- clear-cut color changes in the clinically significant range
- avoids trace reactions that confuse the clinical picture
- close correlation with quantitative tests

AMES COMPANY, INC • ELKHART, INDIANA
Ames Company of Canada, Ltd., Toronto

05554

CAMBRIDGE

AUDIO-VISUAL HEART SOUND RECORDER

"SIMPLI-SCRIBE" DIRECT WRITING ELECTROCARDIOGRAPH

A LOGICAL COMBINATION

While both of these fine instruments are effectively used independently, when used together they provide a new and valuable approach to the more accurate diagnosis of heart disease.

The CAMBRIDGE AUDIO-VISUAL HEART SOUND RECORDER is a radically new portable instrument which enables the Doctor to HEAR, SEE and permanently RECORD heart sounds—simultaneously.

Heart sounds, picked up by the microphone, are amplified to any desired degree for auscultation. The Physician hears the heart tones faithfully reproduced through an electrical stethophone fitted with binaural ear pieces similar to those he is accustomed to using. The heart sounds being heard are simultaneously visible upon the long persistence screen of a three inch cathode ray tube.

Any portion of the heart sounds may be permanently recorded upon paper-thin magnetic discs that may be filed with the patient's history or mailed to a consultant. They may be "played-back" (both heard and viewed) at any time for review, study or consultation.

The CAMBRIDGE "SIMPLI-SCRIBE" Model is a direct writing, portable electrocardiograph. When used in combination with the Audio-Visual Recorder, the electrocardiogram from the "Simpli-Scribe" may be viewed upon the cathode ray screen of the Recorder while listening to the heart sounds, or the electrocardiogram may be superimposed upon the heart sound trace for timing complex cases.

Now the Physician, Hospital or Clinic has available a pair of complementary instruments making possible more rapid, accurate and complete diagnosis of heart disease.

Send for Bulletin 185

CAMBRIDGE INSTRUMENT CO., Inc.

3744 Grand Central Terminal, New York 17, N. Y.
Chicago 39, 4000 West North Avenue
Philadelphia 4, 135 South 36th Street
Cleveland 15, 1720 Euclid Avenue
Detroit 2, 7410 Woodward Avenue

PIONEER MANUFACTURERS OF THE ELECTROCARDIOGRAPH

CAMBRIDGE
CARDIAC DIAGNOSTIC INSTRUMENTS

Effective New Therapy

For Constipation

Revealed in Hospital Research Report

DANNON Prune Whip YOGURT successful in 95% of chronic cases when taken every night for 3 weeks

An important study of chronic constipation at a New York hospital discloses these striking results:*

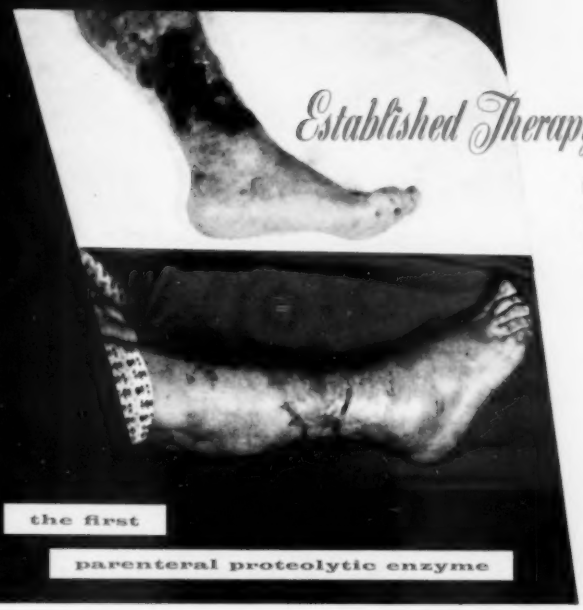
> In a group of 194 chronically ill patients, averaging 71.6 years of age, regular feeding of Dannon Prune Whip Yogurt produced excellent results. Completely normal bowel habits were re-established in 187 patients, or 95.8%. They required no laxatives during the period of administration. Improvement in skin tone, seborrheic dermatitis, intestinal stasis and pruritus ani were also noted.

Here is a natural, physiological approach which offers an effective solution to the widespread problem of faulty evacuation.

Dannon Prune Whip Yogurt is a smooth, custard-like milk food—highly palatable. Made from fresh milk, with about 50% of the butterfat removed, it is low in calories, high in nourishment and has the delicious flavor of old-fashioned prune whip. You may recommend Dannon Prune Whip Yogurt for your most stubborn constipation cases with the same gratifying results described in the above report. Prescribed regimen is to eat one container nightly before bedtime, for three weeks.

For literature, write Dannon Milk Products, Inc., 22-11 38th Avenue, Long Island City 1, N.Y.

*Ferrer, F. P., and Boyd, L. J.: Am. J. Dig. Dis., 22:272, 1955



the first

parenteral proteolytic enzyme

Established Therapy in Vascular Trauma

Female diabetic, 72 years old. Peripheral arteritis obliterans, with cellulitis and gangrenous ulcerations. Burning pain.

Time between photos 9 weeks.

PARENZYME administered daily. Healing of ulcer complete. Pain and edema eliminated.

In decay processes of inflammatory origin with burning pain, swelling and cellular necrosis, PARENZYME's direct proteolytic action alters the chemical and enzymatic phase of circulatory stasis. The integrity of the local circulation is re-established permitting all physiologic processes of repair to proceed unimpeded.[1,2]

PARENZYME®

INTRAMUSCULAR TRYPSIN

is indicated in a wide range of inflammatory disorders characterized by edema.

TRAUMATIC WOUNDS: slow-healing wounds, bruises, contusions, black eyes. VASCULAR DISORDERS: phlebitis, thrombophlebitis, phlebothrombosis. SKIN ULCERS: decubitus, diabetic, varicose. OPHTHALMIC DISORDERS: iritis, iridocyclitis, chorioretinitis.

PARENZYME is safe and has no anticoagulant effect, and is compatible with antibiotics.

Clinical and experimental evidence of PARENZYME's potent therapeutic action has been established in over 16 scientific published papers. Reprints are available upon request.

DOSAGE: 2.5 mg. (0.5 ml.) intragluteally q. 6 h. until improvement results; q. 12 h. thereafter.

Recommended method of injection: very slowly intragluteally.

SUPPLIED: 5 ml. multiple-dose vials (5 mg. trypsin/ml.).

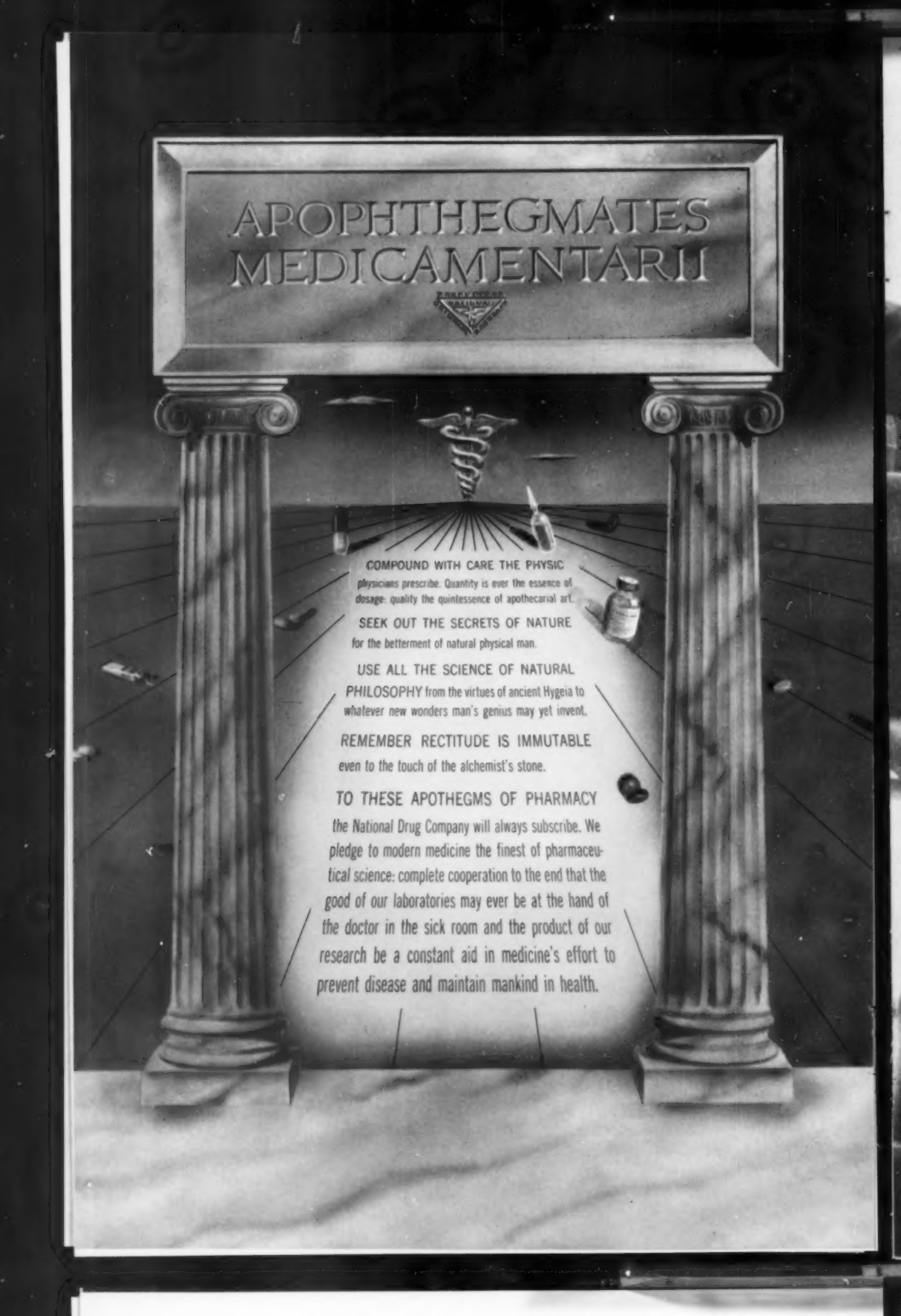
REFERENCES: 1. Wildman, C. J.: Angiology 6:473, 1955. 2. Seligman, B.: Ohio State Med. J. 51: 442, 1955.

The film "CLINICAL ENZYMOLOGY" is now available for showing at medical meetings upon your request. And be sure to watch for the MED-AUDIOGRAPHS, a series of recorded clinical discussions.

PRODUCTS OF ORIGINAL RESEARCH

NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL NATIONAL

THE NATIONAL DRUG COMPANY PHILADELPHIA 44, PA.


APOPHTHEGMATES
MEDICAMENTARII
COMPOUND WITH CARE THE PHYSIC
physicians prescribe. Quantity is ever the essence of dosage: quality the quintessence of apothecarial art.
SEEK OUT THE SECRETS OF NATURE
for the betterment of natural physical man.
USE ALL THE SCIENCE OF NATURAL PHILOSOPHY from the virtues of ancient Hygeia to whatever new wonders man's genius may yet invent.
REMEMBER RECTITUDE IS IMMUTABLE
even to the touch of the alchemist's stone.
TO THESE APOTHEGMS OF PHARMACY
the National Drug Company will always subscribe. We pledge to modern medicine the finest of pharmaceutical science: complete cooperation to the end that the good of our laboratories may ever be at the hand of the doctor in the sick room and the product of our research be a constant aid in medicine's effort to prevent disease and maintain mankind in health.

for petit mal epilepsy

a drug of choice in initiating treatment[1]

MILONTIN®

Kapseals® and Suspension

(methylphenylsuccinimide, Parke-Davis)

Specifically valuable for control of petit mal attacks...of definite help in some patients with psychomotor seizures[1-5]...often effective in patients refractory to other therapy[4-6]...with few mild side effects[1-6]... *and after five years of study, found least toxic of all effective drugs.*[1]

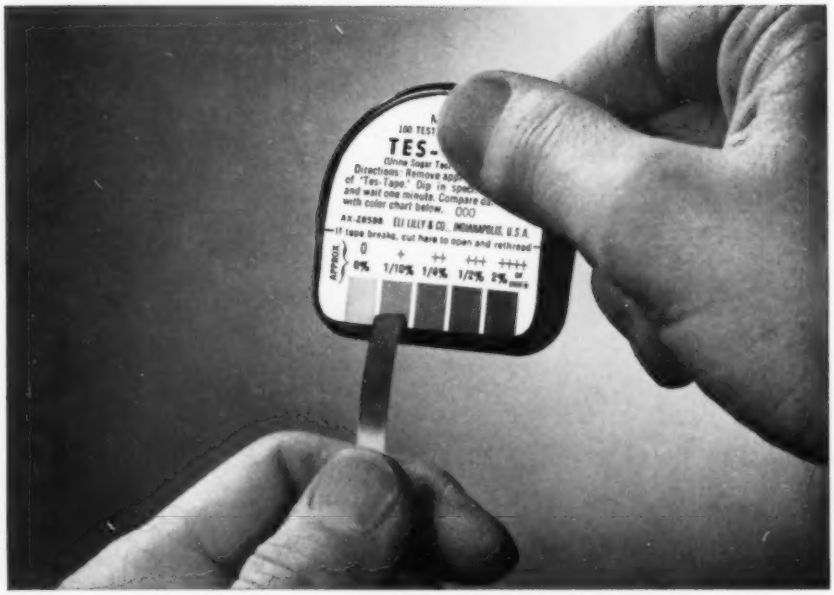
In patients with mixed grand mal–petit mal epilepsy, its compatibility permits use of MILONTIN with Dilantin® Sodium (diphenylhydantoin sodium, Parke-Davis) or with Dilantin Sodium with Phenobarbital.

MILONTIN Kapseals, 0.5 Gm., bottles of 100 and 1,000; also available as MILONTIN Suspension (250 mg. per 4-cc. tsp.) in 16-ounce bottles. Detailed information available upon request, or from your Parke-Davis representative.

(1) Zimmerman, F. T.: *New York J. Med.* 55:2338, 1955. (2) Carter, C. H.: *Neurology* 4:935, 1954. (3) Forrer, G. R.: *J. Michigan M. Soc.* 53:275, 1954. (4) Smith, B., & Forster, F. M.: *M. Ann. District of Columbia* 22:279, 1953. (5) Lemere, F.: *Northwest Med.* 53:482, 1954. (6) Davidson, D. T., Jr.: Lombroso, C., & Markham, C. H.: *New England J. Med.* 253:173, 1955.

PARKE, DAVIS & COMPANY DETROIT, MICHIGAN

80006



NEW

urine sugar test of unmatched simplicity

'Tes-Tape'

(URINE SUGAR TEST TAPE, LILLY)

'Tes-Tape' completely eliminates the need for test tubes, heat, reagents, or any other paraphernalia in quantitative urine sugar determinations. Simply moisten a strip of 'Tes-Tape' with the specimen. After just sixty seconds, compare it with the color chart on the 'Tes-Tape' dispenser. Then read off the percentage of sugar. The selective action of 'Tes-Tape' prevents false positive reactions, assures complete accuracy.

The convenient size of the 'Tes-Tape' dispenser permits you to carry it on house calls for on-the-spot determinations. Your patients also will welcome the convenience, simplicity, and accuracy of 'Tes-Tape.'

Now available at pharmacies everywhere.

Lilly

QUALITY / RESEARCH / INTEGRITY

ELI LILLY AND COMPANY • INDIANAPOLIS 6, INDIANA, U.S.A.

626050

80th ANNIVERSARY 1876 • 1956

SECOND SERIES MAY 1956 VOL. 32, NO. 5

BULLETIN OF THE NEW YORK ACADEMY OF MEDICINE

CONTENTS

The Nature of the Response to Stress with Aging . . 329
James L. Whittenberger

Gastrointestinal Hemorrhage in Elderly Patients . . 337
Thomas P. Almy, David M. Roseman and Warren S. Braveman

The Romantic Period in Medicine 346
Iago Galdston

Management of Pancreatitis: Acute and Chronic . . 363
Transcription of a Panel Meeting on Therapeutics
Charles F. Wilkinson, Jr., J. William Hinton, Michael Lake and Milton R. Porter

New York Pathological Society: Abstracts 386

AUTHORS ALONE ARE RESPONSIBLE FOR OPINIONS EXPRESSED IN THEIR CONTRIBUTIONS

ROBERT L. CRAIG, *Editor*

Published Monthly by THE NEW YORK ACADEMY OF MEDICINE
2 East 103 Street, New York 29, N. Y.

Annual subscription United States and Canada $6.50. All other countries $7.50. Single copies 75c.
ADVERTISING OFFICE • 30 ROCKEFELLER PLAZA, N. Y. C. 20 • CIRCLE 7-7706
Copyright, 1956 by The New York Academy of Medicine

OFFICERS AND STAFF OF THE ACADEMY

1956

President

EDWARD J. DONOVAN

Vice-Presidents

JEROME P. WEBSTER — ROBERT L. LEVY — HAROLD BROWN KEYES

Treasurer

SHEPARD KRECH

Recording Secretary

FREDERICK H. WILKE

Trustees

GEORGE BAEHR	*SHEPARD KRECH	HENRY ALSOP RILEY
BRADLEY L. COLEY	ASA L. LINCOLN	BENJAMIN P. WATSON
CONDICT W. CUTLER, JR.	WILLIAM F. MACFEE	ORRIN S. WIGHTMAN
*EDWARD J. DONOVAN	HAROLD R. MIXSELL	*FREDERICK H. WILKE
	WILLIAM BARCLAY PARSONS	

Council

The President — The Vice-Presidents — The Trustees
The Treasurer — The Recording Secretary
The Chairmen of Standing Committees

Director

HOWARD REID CRAIG

Librarian

JANET DOE

Executive Secretary
Committee on Public Health

HARRY D. KRUSE

Executive Secretary
Committee on Medical Education

ROBERT L. CRAIG

Executive Secretary
Committee on Medical Information

IAGO GALDSTON

Comptroller

ARTHUR A. EBERLE

Legal Counsel

DAVIS POLK WARDWELL SUNDERLAND & KIENDL

Library Consultants

B. W. WEINBERGER, CURT PROSKAUER

EDITORIAL BOARD

JEROME P. WEBSTER, *Chairman*	JANET DOE
DAVID P. BARR	JOHN G. KIDD
MARGARET BEVANS	ROBERT F. LOEB
WILLIAM DOCK	LOUIS M. ROUSSELOT

ROBERT L. CRAIG, *Secretary and Editor*

* Ex-officio

BULLETIN OF
THE NEW YORK ACADEMY
OF MEDICINE

VOL. 32, NO. 5 MAY 1956

THE NATURE OF THE RESPONSE TO STRESS WITH AGING*

The Harlow Brooks Lecture

JAMES L. WHITTENBERGER

Professor of Physiology, Harvard School of Public Health, Boston, Massachusetts

I DEEPLY appreciate the honor accorded by the invitation to deliver the Harlow Brooks Lecture in this Graduate Fortnight. During its preparation I have felt a sense of inadequacy to develop the subject in a way which would do honor to the memory of Dr. Brooks.

In order to confine the subject to reasonable bounds, one must begin by limiting the meaning of words used in the title. In recent years many diseases have come to be called diseases of adaptation, or at least to contain elements which represent failure of adequate response to stress; the stress may be anything from a virus infection to a conflict situation.[1] As emphasized in a recent publication of The New York Academy of Medicine,[2] disease is best understood as the result of multiple causes, those pertaining to the reactions of the host, or patient, and those pertaining to the environment. The environment is defined broadly, to include not only microorganisms and the physical sur-

* Presented before the 28th Graduate Fortnight on *Problems of Aging*, at The New York Academy of Medicine, October 17, 1955.

roundings, but also the social habitat of the patient. Stress occurs in the interactions of man with all of these components of the environment.

The term stress has many meanings. Writers who take pains to define it in discussions of psychosomatic medicine ordinarily use the mechanical definition,—an external force. Some continue the analogy by using the term *strain* to identify the response or deformation produced by the stress. However, most writers do not distinguish between stress and strain, and call the effect on the organism *stress*. The latter usage is also correct by another definition in Webster's Dictionary. The result is, of course, confusion. I shall try to minimize confusion tonight by avoiding areas which I do not feel competent to discuss, for example, the field of stress psychology.

Biologically, excitability or irritability in response to a change in the environment is a fundamental characteristic of all living organisms. The organism cannot be isolated from an environment which is usually changing in some respect; therefore life is a continuous series of stimulus-response or stress-strain relationships. As one eminent physiologist remarked, a man not under stress is one in bed, asleep and not having dreams. Even this example is questionable if one accepts a change of the "internal environment" as a "stress." Clearly an acceptable definition and classification of stresses would be helpful in developing understanding of this complex field.

Of greatest interest to many people is the stress or strain related to emotions; the same endocrine and neural mechanisms may be called into play as in the response to physical stress with similar effects on blood sugar, blood pressure, and other attributes. Based fundamentally on the concepts of Walter Cannon and earlier physiologists, a great expansion of research in this field has occurred. The term homeostasis, introduced by Cannon to describe the "steady state" tendencies of body mechanisms, has been exalted and widely used in ways never visualized by Cannon. The term has been used generally to indicate a departure from a position of stability; the *status quo* might refer to a state of health or to a period of "well-being" in a society. Such developments of a concept appear warranted only if their applicability is soundly established. Disease has been called a failure of homeostasis, without a serious attempt to elucidate the possible mechanisms involved. It must be recognized that we are only at the beginning of an understanding of the mechanisms that operate in the adaptation of the human being

to the stresses which constitute life experience.

The significance of homeostasis itself is not always clear. We for example maintain our alveolar CO_2 tension in a narrow range about 40 mm. Hg at sea level. After acclimatization to higher altitude, the alveolar CO_2 tension may be held with equal precision at 30 mm. Hg. The reasons for this adaptation are evident, but the point is that the body functions as well at a CO_2 tension of 30 as at 40 mm. Hg. Although the advantages of a steady state are thus obtained at a lower level of CO_2 pressure, it should be added that this is accomplished at the cost of greater respiratory work and a loss of potential reserve.

Sudden changes in bodily states are most detrimental, and as Barcroft[3] pointed out only the highest functions of the central nervous system are affected by small deviations of acidity, blood glucose, temperature, and other attributes. Other organs in general can function satisfactorily over a much wider range of variability of the internal environment.

The quantitative relationships between stress and disturbance of homeostasis are difficult to assess. In exposure to environmental heat, for example, the change of body temperature is a measure of *failure* of adaptation, since the slightest rise of blood temperature normally activates sweating and other mechanisms of heat loss, and body temperature is stabilized. The reactivity of the organism can be measured, however, by noting the severity of environmental conditions necessary to cause a given increment of body temperature, or preferably, by measuring the changes in specific avenues of heat loss, such as the rate of evaporation of sweat.

A further difficulty in interpreting responses to environmental stress is illustrated by the fact that a successful attainment of objective, such as a stable body temperature, may be obtained by different combinations of adaptive reactions. A young individual may sustain thermal equilibrium in the cold by minor contributions from several compensatory mechanisms; the elderly may have impairment of one or more of these mechanisms, yet sustain thermal balance by proportionately greater utilization of the remainder.

The mechanisms of reaction to stress include the autonomic nervous system, the hypothalamic-pituitary-adrenal system, non-endocrine humoral factors, and probably some unknown factors. Reactions to stress are of two kinds, the specific and the general. Specific reactions

roundings, but also the social habitat of the patient. Stress occurs in the interactions of man with all of these components of the environment.

The term stress has many meanings. Writers who take pains to define it in discussions of psychosomatic medicine ordinarily use the mechanical definition,—an external force. Some continue the analogy by using the term *strain* to identify the response or deformation produced by the stress. However, most writers do not distinguish between stress and strain, and call the effect on the organism *stress*. The latter usage is also correct by another definition in Webster's Dictionary. The result is, of course, confusion. I shall try to minimize confusion tonight by avoiding areas which I do not feel competent to discuss, for example, the field of stress psychology.

Biologically, excitability or irritability in response to a change in the environment is a fundamental characteristic of all living organisms. The organism cannot be isolated from an environment which is usually changing in some respect; therefore life is a continuous series of stimulus-response or stress-strain relationships. As one eminent physiologist remarked, a man not under stress is one in bed, asleep and not having dreams. Even this example is questionable if one accepts a change of the "internal environment" as a "stress." Clearly an acceptable definition and classification of stresses would be helpful in developing understanding of this complex field.

Of greatest interest to many people is the stress or strain related to emotions; the same endocrine and neural mechanisms may be called into play as in the response to physical stress with similar effects on blood sugar, blood pressure, and other attributes. Based fundamentally on the concepts of Walter Cannon and earlier physiologists, a great expansion of research in this field has occurred. The term homeostasis, introduced by Cannon to describe the "steady state" tendencies of body mechanisms, has been exalted and widely used in ways never visualized by Cannon. The term has been used generally to indicate a departure from a position of stability; the *status quo* might refer to a state of health or to a period of "well-being" in a society. Such developments of a concept appear warranted only if their applicability is soundly established. Disease has been called a failure of homeostasis, without a serious attempt to elucidate the possible mechanisms involved. It must be recognized that we are only at the beginning of an understanding of the mechanisms that operate in the adaptation of the human being

to the stresses which constitute life experience.

The significance of homeostasis itself is not always clear. We for example maintain our alveolar CO_2 tension in a narrow range about 40 mm. Hg at sea level. After acclimatization to higher altitude, the alveolar CO_2 tension may be held with equal precision at 30 mm. Hg. The reasons for this adaptation are evident, but the point is that the body functions as well at a CO_2 tension of 30 as at 40 mm. Hg. Although the advantages of a steady state are thus obtained at a lower level of CO_2 pressure, it should be added that this is accomplished at the cost of greater respiratory work and a loss of potential reserve.

Sudden changes in bodily states are most detrimental, and as Barcroft[3] pointed out only the highest functions of the central nervous system are affected by small deviations of acidity, blood glucose, temperature, and other attributes. Other organs in general can function satisfactorily over a much wider range of variability of the internal environment.

The quantitative relationships between stress and disturbance of homeostasis are difficult to assess. In exposure to environmental heat, for example, the change of body temperature is a measure of *failure* of adaptation, since the slightest rise of blood temperature normally activates sweating and other mechanisms of heat loss, and body temperature is stabilized. The reactivity of the organism can be measured, however, by noting the severity of environmental conditions necessary to cause a given increment of body temperature, or preferably, by measuring the changes in specific avenues of heat loss, such as the rate of evaporation of sweat.

A further difficulty in interpreting responses to environmental stress is illustrated by the fact that a successful attainment of objective, such as a stable body temperature, may be obtained by different combinations of adaptive reactions. A young individual may sustain thermal equilibrium in the cold by minor contributions from several compensatory mechanisms; the elderly may have impairment of one or more of these mechanisms, yet sustain thermal balance by proportionately greater utilization of the remainder.

The mechanisms of reaction to stress include the autonomic nervous system, the hypothalamic-pituitary-adrenal system, non-endocrine humoral factors, and probably some unknown factors. Reactions to stress are of two kinds, the specific and the general. Specific reactions

may be illustrated by the development of specific antibodies to infectious antigens, or by the building of tolerance to toxic chemicals. The *general* response is entirely non-specific and directly or indirectly involves most if not all the tissues of the body.[4] The response may be elicited by many types of stimuli or stresses,—anxiety, fear, surgical operations, anoxia, and so on. The sympathetic-adrenal system is activated, causing mobilization of blood glucose, acceleration of heart rate, skeletal muscle tensing, changes of gastrointestinal motility and secretions, and other activities which prepare the organism for "fight or flight." Cannon demonstrated beautifully in the cat that total sympathectomy seriously impaired the reactions to stress. What is less well known is that the dog is affected by sympathectomy very much less than the cat, and that man is probably much closer to the dog in his post-sympathectomy behavior.[4]

Equally fundamental in the general response to stress is the activation of the pituitary-adrenal cortex mechanism. Many details are unknown, but it is clear that tissue reactions to stress require the presence of adrenal cortical hormone, and that the elaboration of hormone is roughly proportional to the degree of stress. Increased production of adrenocorticotropin by the anterior pituitary and adrenal cortical hormone by the adrenal cortex occur very rapidly in response to stress. Many of the peripheral effects are now well known,—the early excess of protein catabolism, retention of sodium, lymphocytopenia, and so on. However, not all of the phenomena of reactions to stress can be explained on the basis of existing knowledge of either the sympathetic or the pituitary-adrenal cortex systems.

With this confession of our state of ignorance I should like to proceed to examine some of the evidence that the response to stress varies with age and to evaluate if possible the impairment which results from these changes.

One of the stresses which is a part of daily life is that of muscular exercise. Exercise is on the one hand a component of play and on the other hand may be the cause of the general adaptation syndrome as conceived by Selye.[5] The disturbances in the fluid matrix of the body resemble those caused by anoxia, high environmental temperature, and other stresses. Various emotions are associated with exercise, from pleasure to anger and pain. Many believe that physical exercise causes dissipation of anxiety and other undesirable emotions. Unfortunately

the contributions of emotion to the physiologic and biochemical characteristics of exercise cannot be precisely measured. It is also probable that the emotional undercurrents of exercise change with age and the development of character. For example, the alteration of motivation with advancing age is a commonly recognized difficulty in attempts to assess the work or exercise capacity of elderly individuals.

The physiologic reactions to exercise stress involve all the homeostatic mechanisms of the body; the integrated responses limit the departures from a steady state in body tissues. The increase of respiratory minute volume is normally in proportion to the metabolic increase and thereby the O_2 supply and pH are held near normal. The heart and blood vessels are an integral part of this response, and they in addition effectively maintain the body temperature almost constant by increasing heat loss from the skin.

There is no need to list in detail the responses to this universally experienced stress. Certain features, however, are illuminating in relation to long-term adaptation and efficiency of performance at different ages. First, there is a large element of variability in genetic endowment. After equal amounts of training, a marathon runner like Clarence DeMar can perform a given task with lower than average demand on the O_2 exchange and transport mechanisms.[6] I have been informed that not until DeMar was over sixty did his cardiovascular responses to exercise become like those of an average man in his prime.

Though physiologic capacities like those of DeMar occur only rarely, every man can improve his performance by practice. Regular regimens of exercise lead, within limits, to improved levels of physical fitness. Americans, it might be noted, are not remarkable for high levels of physical fitness. Whether this general lack of physical fitness is related to longevity or to frequency and severity of coronary artery disease is an unsettled question. It does appear that sudden stresses of physical activity are better tolerated in persons whose physical fitness has been kept high by regular activities.

It is common knowledge based on athletic performances and on personal observation that peak capacities fall away perceptibly after the age of about 30 years. Regardless of whether one attributes senescence to genetically based involution or to the progressive accumulation of minor injuries, there is no doubt that physiologic capacities in general deteriorate with age. There is uncertainty about the exact shape

of the senescence curve of a given individual or a given system, but when cross-sectional samples are taken at different ages, it is found that many physiologic functions decline in a nearly rectilinear manner with age. There are exceptions, of course, in individual tissues and systems, and the variability of observations seems to increase with age.

In response to stresses like exercise, many factors contribute to progressive impairment with advancing age. Other speakers in this series have dealt or will deal with reaction to other stresses such as those of general anesthesia and major surgery. In a sense the result of senescence can be called a loss of functional reserve of the component systems. In a complex stress situation such as severe exercise, the several decrements may be compounded in their effects on performance. The pumping capacity of the heart and the distensibility of blood vessels are reduced as age increases;[7] at the same time the resistance of vascular beds increases. The skin and its heat exchange mechanisms become atrophic. It is not surprising that Robinson's subjects aged 63 were able to increase their O_2 uptake during exercise to only 2/3 of the level attained by young men.[8]

The aging of homeostatic mechanisms has been described as a loss of flexibility in response to changes in the environment.[9] Under conditions of normal stress the body temperature, the pH of the blood, and other attributes of the internal environment are normal. Impairment becomes evident only when the ability to withstand extremes of temperature is called upon.[10] Some of the evidence cited for this statement is the accumulation of older persons in balmy southern climates and the avoidance of "hot jobs" such as those in a steel rolling mill. However, other explanations of these phenomena are pertinent, and there is little experimental evidence for physiologic impairment of heat regulation. Horvath et al.[11] recently found that their elderly subjects were less uncomfortable at 10°C than young subjects. Shivering occurred later and less commonly in the elderly subjects, yet their body temperatures did not fall during exposures of approximately half an hour.

It is everyone's experience to know old people who are intellectually and physically vigorous in their 80's, and others who are physiologically senile at 60. With such a wide spread, it isn't surprising that studies have shown much variability in capabilities of the aged.

Comparisons are sometimes made between elderly, hospitalized, sedentary patients and healthy young volunteers who lead an active

life. Some of the studies on responses of the elderly are probably more influenced by atrophy of disuse than by inherent involution of body tissues. One of the fundamental truths of biology is that maintenance of function and structure depend upon continued use of that function. Often the capacity of a system is directly proportional to the vigor of the demands made upon it. One does not acclimatize to summer heat by sitting in the shade. By approaching the limits of performance daily one can greatly improve his capacity for work output in the heat.

A word should be said about time relationships of adaptation in the senescent individual. With further reference to the athletic performer, it is noted that a baseball pitcher needs increasing rest intervals between appearances as he approaches the end of his baseball career—he requires four or five days of rest instead of two or three. More continuous attention is needed to maintain good physical condition, and, once lost, longer time is required to regain top condition. This is true of us all. After the age of 40, an active weekend no longer serves to maintain physical capacity. In the words of Harlow Brooks[12] "regular temperate exercise, suitable to the age and condition of training should be maintained."

Similarly, an elderly patient is slower to convalesce. Muscle mass and bone matrix, lost during bed rest, are restored more slowly and less completely in elderly individuals.

Much has been written about the aging of endocrine mechanisms, as exemplified by the slow decrease of metabolic rate and 17-ketosteroid excretion with age. Knowledge of endocrine changes with age is fragmentary. The slow fall of metabolic rate and the more definite fall of 17-ketosteroid excretion might suggest a deterioration of anterior pituitary function. However, the aging pituitary continues to form gonadotropins, and the adrenocorticotropin output in response to stresses like surgical operations is almost if not wholly normal. The decrease of metabolism with age does not occur in other animals, and there is doubt of its significance in man. When correlated with an index of active tissue, such as intracellular water, there may be no decrease of metabolic rate.[9]

The shortcomings of our appraisal of reactions to stress do not prove that impairments with age do not contribute to the rapidly increasing susceptibility to the forces of mortality which characterize the later years of life. Many of these, such as arteriosclerosis, represent

cumulative effects, which require a long time to develop into forces of mortality. Such pathologic changes not only represent internal threats to homeostasis, but also handicap the mechanisms of adaptation.

In summary, the complexities of reaction to stress have been emphasized. The impairment with age is real, but the results are not necessarily serious, as long as internal and external stresses are reduced in proportion to diminished adaptive capacities of the aged. Compensatory mechanisms and experience minimize the results of physiologic limitations but more and more of these factors are called into play as the organism ages. Much could be done in preservation of function of the elderly, if attention were paid to maintenance of high levels of mental and physical activity. The organism will eventually "run down" as physiologic reserves are exhausted but meanwhile everything possible will have been done to make life not only longer but more satisfying.

REFERENCES

1. *Beyond the germ theory; the roles of deprivation and stress in health and disease,* Iago Galdston, editor. New York, Health Education Council, 1954.
2. *Epidemiology (The) of health,* Iago Galdston, editor. New York, Health Education Council, 1953. (New York Academy of Medicine book.)
3. Barcroft, (Sir) J. *Features in the architecture of physiological function.* Cambridge, England, University Press, 1934.
4. Sayers, G. Adrenal cortex and homeostasis, *Physiol. Rev. 30*:241-320, 1950.
5. Selye, H. Stress and disease, *Science 122*:625-31, 1955.
6. Dill, D. B., Talbot, J. H. and Edwards, H. T. Studies in muscular activity; response of several individuals to a fixed task, *J. Physiol. 69*:267-305, 1930.
7. Landowne, M., Brandfonbrener, M. and Shock, N. W. The relation of age to certain measures of performance of the heart and the circulation, *Circulation 12*:567-76, 1955.
8. Robinson, S. Experimental studies of physical fitness in relation to age, *Arbeitsphysiologie 10*:251-323, 1938.
9. Shock, N. W. Ageing of homeostatic mechanisms, in *Cowdry's problems of ageing,* (A. I. Lansing, ed.) 3.ed. Baltimore, Williams and Wilkins Co., 1952, pp. 415-446.
10. Carlson, A. J. and Stieglitz, E. J. Physiological changes in aging, *Ann. Amer. Acad. polit. soc. Sci. 279*:18-31, 1952.
11. Horvath, S. M., Radcliffe, C. E., Hutt, B. K. and Spurr, G. B. Metabolic responses of old people to a cold environment, *J. appl. Physiol. 8*:145-48, 1955.
12. Brooks, H. Heart of the athlete, in *Contributions to the medical sciences in honor of Dr. Emanuel Libman,* New York, International Press, 1932, v. *I,* pp. 227-240.

GASTROINTESTINAL HEMORRHAGE IN ELDERLY PATIENTS*

THOMAS P. ALMY, DAVID M. ROSEMAN and WARREN S. BRAVEMAN

IN THE medical services of civilian hospitals, an outstanding opportunity to study the circulatory disturbances in hemorrhagic shock is afforded by cases of gastrointestinal bleeding. This is particularly true in elderly patients, in whom the consequences of hemorrhage are more severe and the high mortality rate has been repeatedly emphasized.[1] Formerly this was due to simple exsanguination, the compensatory circulatory readjustments being inadequate, in these elderly arteriosclerotic individuals, to maintain the circulation of heart and brain. Now, with the increasing availability of bank blood in large quantities, the dangers seem to lie at least partly in the prolonged operation of these compensatory mechanisms, which results in deprivation of blood from such organs as the liver and kidney. It is the purpose of this paper to call attention to a variety of clinical consequences of gastrointestinal hemorrhage, some of which are due to the failure of these compensations, and others to their prolonged operation. Each of these syndromes seems attributable to acute or chronic ischemia of a specific organ, and seems understandably related to the overall pattern of vascular readjustment in shock.

The adaptation to acute blood loss in man depends little upon the release of blood from the spleen and other reservoirs, the capacity of which is small; and little upon hemodilution, which takes many hours to be effective. The major adjustment is the redistribution of blood brought about by differential constriction in various portions of the vascular bed. Thus with a loss of about 20 per cent of the total blood volume, splanchnic blood flow, especially to the kidney and liver, may be sharply restricted. This mechanism is so efficient that the blood pressure and pulse may be unchanged and the skin may remain dry,

* Presented at the 28th Graduate Fortnight on *Problems of Aging*, of The New York Academy of Medicine, October 12, 1955.

From the Second (Cornell) Medical Division, Bellevue Hospital, and the Department of Medicine, The New York Hospital-Cornell Medical Center, New York.

and of normal warmth and color. In such a case the clinical signs of shock are absent. With hemorrhages of greater magnitude the blood flow through the skin and peripheral muscles is also diminished, the signs of shock then appear, and even the carefully guarded coronary and cerebral circulations may become impaired.[2]

Many factors contribute to the total effect on vital organs of the ischemia resulting from hemorrhage. Even in healthy young experimental subjects, hepatic blood flow, once reduced by venesection, has been shown to remain low for some time after the drawn blood has been restored to the circulation.[3] With slowing of the circulation in both arteries and veins the likelihood of intravascular thrombosis is increased. With increasing arteriosclerosis in elderly patients, it is expected that the redistribution of blood by differential vasoconstriction will be less efficient, and vital organs will become more severely ischemic than in younger persons having the same degree of hemorrhage. The degree of anoxia to which a given organ is subjected will be determined in addition by the chance occurrence of atheromatous plaques, which would reduce blood flow to the organ even in the absence of hemorrhage. The capacity of the organ to function at low oxygen tension may have been impaired by the accumulation of earlier injuries from other causes, as one finds in the kidney in chronic pyelonephritis, or in the liver in nutritional cirrhosis.

We attribute to the combined effects of these various factors the considerable variety of clinical syndromes which we find in elderly patients who have survived the acute phase of gastrointestinal hemorrhage. The cases to be described have all been encountered in the last few years on the medical services of Bellevue Hospital, The New York Hospital, and The Manhattan Veterans Hospital.

Case 1: *Acute Renal Failure:*

A 73 year old man, known previously to be hypertensive but having a normal blood NPN and urinalysis, was admitted to Bellevue Hospital for Ménière's syndrome, for which a section of the VIIIth nerve was performed. The day after operation he developed acute gastrointestinal hemorrhage with shock. Transfusions relieved the appearances of shock in a few hours, but the blood pressure did not return to the previous hypertensive levels for two days and the urinary output was suppressed for eleven days. The blood NPN rose to 100 on the second day after the hemorrhage, and to 300 on the seventh day. Three months later it had returned to normal, and the concentrating power of the kidney was restored. The source of bleeding could never be found on x-rays, and the hemorrhage has not recurred.

It is widely recognized that some degree of azotemia occurs even in mild hemorrhages. This is partly because of absorption of nitrogen

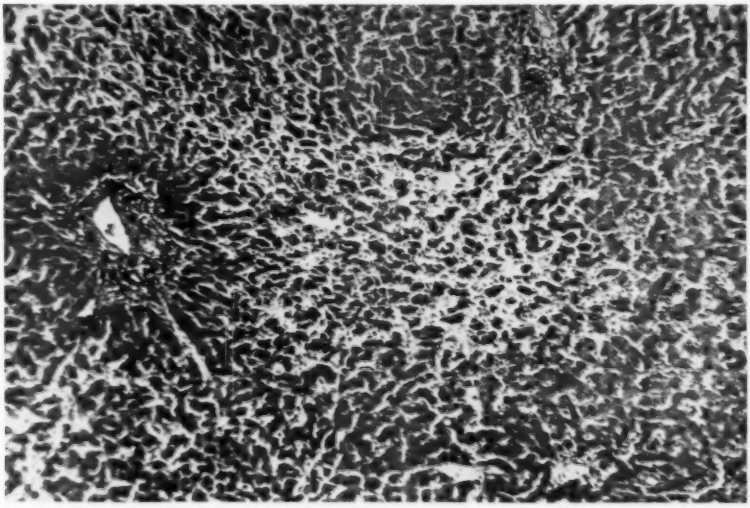


Fig. 1—Low power view (hematoxylin and eosin stain) showing an area of focal hepatic necrosis (Case No. 2).

from the intestine and partly because of acute renal insufficiency.[4] Clinically one finds greater degrees of azotemia in those patients with pre-existing disease processes affecting the kidney,—the most common examples are pyelonephritis, nephrosclerosis with hypertension and obstructive uropathy due to nodular hyperplasia of the prostate. We have seen azotemia persist for one year after a gastrointestinal hemorrhage, with ultimate return of normal renal function.

Case 2: *Acute Hepatic Decompensation:*

A 52 year old man was admitted to Bellevue Hospital because of hematemesis for one day. On examination he had a normal mental status, no icterus, and no signs of shock. His serum albumin was 4.2 gm. and his globulin 1.5. Cephalin flocculation reaction was 0, alkaline phosphatase 2.8 Bodansky units, and icterus index 10. His blood pressure was maintained by transfusion, in spite of repeated vomiting of blood. After 24 hours, in the belief that he had a peptic ulcer, a laparotomy was performed. No ulcer was found, but a hard nodular liver and an enlarged spleen were present. The portal pressure was elevated to 422 mm. of saline, but a portacaval shunt was considered inadvisable at that time. Following operation, esophageal balloon tamponage was established, and the bleeding ceased; but by the seventh postoperative day the alkaline phosphatase had risen to 5.6 and the icterus index to 35. On that day he again vomited blood. The next day he was comatose, though his blood pressure was normal. The following day he died. At autopsy the liver was found to have numerous areas of acute focal necrosis as well as the chronic changes observed at operation. The microscopic section strikingly demonstrates this acute injury (Fig. 1).

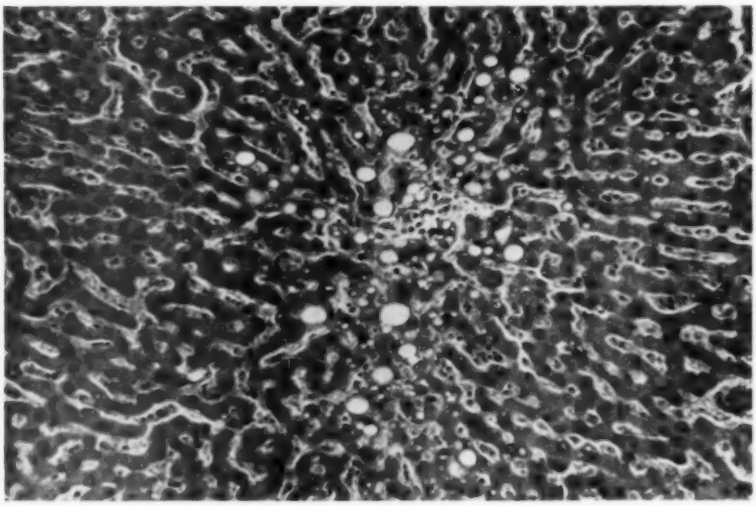


Fig. 2—Case of a 64 year old man who sustained a fatal hemorrhage from a duodenal ulcer. Low power view (hematoxylin and eosin stain) showing cytoplasmic vacuoles in the liver cells surrounding a central vein.

It is interesting to compare this finding with that in a 64 year old man autopsied at The New York Hospital following fatal hemorrhage from a duodenal ulcer. By gross and microscopic examination the liver was free of cirrhosis or other chronic parenchymal damage. The sections, however, showed many cytoplasmic vacuoles in the liver cells surrounding the central veins (Fig. 2). Similar vacuoles containing no fat or glycogen have been described by others[5] in the liver and other organs of persons dying in states of acute anoxia.

Our cases seem to verify that, both in the presence and in the absence of chronic liver disease, hemorrhage and anoxia may cause an acute liver injury. In average hospital experience this is often evident chemically and sometimes demonstrable pathologically. The clinical effects of this injury will of course be more apparent in those whose reserves of liver function have been reduced by the cumulative damage of years of liver disease.

Case 3: *Gangrene of Foot*:

A 64 year old man was admitted to the Manhattan Veterans Administration Hospital after having had intermittent claudication for two years. Five weeks before admission he had had hematemesis and melena, and at another hospital he had been found to have an anemia and x-ray evidence of a gastric ulcer. He was

transfused, and for the next several weeks a normal hemoglobin was maintained. Nevertheless, during the first week after the hemorrhage, he developed numbness and pain in the right foot, progressing to coldness and discoloration of the toes, so that at the time of admission to the Veterans Hospital his foot was in an advanced state of gangrene. Shortly after admission there he had a recurrent hematemesis, for which an emergency gastrectomy was performed. He died on the ninth postoperative day, and autopsy was not performed.

The gangrene here observed could have been due to simple ischemic necrosis, the result of prolonged peripheral vasoconstriction and diminished blood flow. This process, however, should have been bilateral and accompanied by signs of simultaneous vasoconstriction elsewhere, affecting, for example, the urinary output. It seems more likely, especially considering the earlier syndrome of claudication, that he had a critically reduced arterial circulation in the legs, and that during the period of hypotension and diminished blood flow incident to his first major hemorrhage, a number of intravascular thromboses may have occurred.

Case 4: *Cerebral Vascular Accident*:

A 71 year old man was admitted to Bellevue Hospital because of 12 hours of severe rectal bleeding. He had a history of hypertension and mild congestive heart failure in the past, the latter successfully treated on an ambulatory basis. On admission there were no signs of shock, and the neurological examination was entirely negative. On the fourth day in the hospital, however, he had recurrent rectal hemorrhage with a striking fall in the hematocrit. Within a few hours he showed a right facial palsy. On the next day he appeared markedly lethargic, with a complete right hemiparesis. After this he sank further into coma and died on the eighth day.

It has been shown that the cerebral blood flow may decline significantly during shock.[6] It is probable that in some persons this decline is small enough so that compensatory changes, such as an increase of the cerebral A-V oxygen difference and local vasodilatation, may suffice to prevent prolonged anoxia and hence irreversible damage to cortical areas. In many older persons, however, with pre-existing cerebral arteriosclerosis, acute reduction in cerebral blood flow may bring about arterial thrombosis or simple ischemic necrosis, with clinical results of the kind just described.[7,8]

Case 5: *Myocardial Infarction*:

A 60 year old man had been known for ten years to have diverticulitis of the colon, arteriosclerotic heart disease with angina of effort, and mild congestive failure controlled by digitalis. He was admitted to The New York Hospital because of tarry stools for one week and massive bleeding for one day. Despite transfusion of large amounts of blood, he had further hemorrhage, with persistent hypotension. Six hours after admission he developed crushing substernal pain, radiating to the left shoulder and persisting for several hours. The clinical im-

pression of myocardial infarction was confirmed by typical changes in serial EKG's. Over the next three days he continued to bleed massively. To replace the estimated volume of shed blood and to maintain normal vital signs, 40 units of blood (20 liters) were required. At this time it seemed obvious that the bleeding was unchecked, and we believed that it was coming from the area of diverticulitis in the distal colon. Thus, on the second day after his myocardial infarction, a left hemicolectomy was performed as an emergency, and no further hemorrhage occurred. Postoperatively, he had repeated bouts of auricular flutter and fibrillation, and hypotensive episodes which responded only to nor-epinephrine; there was, however, no electrocardiographic evidence of a new infarct. He developed atelectasis and a right upper lobe pneumonia, superficial thrombophlebitis, and at one point a brief psychotic depression. He nevertheless survived all these complications, returned to his former level of activity outside the hospital, and is presently being followed in the out-patient department.

In the course of shock, the heart is considered to be protected against anoxia through vasoconstriction elsewhere. In animal experiments, however, the coronary blood flow declines significantly during severe but non-fatal hemorrhage.[9] Previous clinical studies in man[10-13] have demonstrated the frequent occurrence of myocardial ischemia in instances of massive gastrointestinal bleeding, especially in the older age groups where some degree of underlying coronary sclerosis is common. EKG abnormalities, anginal chest pain and acute congestive failure have been described. In some cases actual myocardial infarction, with or without fresh coronary thrombosis, may be the sequel of prolonged reduction of coronary blood flow.[14, 15]

Among 200 cases of gastrointestinal hemorrhage reviewed at The New York Hospital, six patients had acute myocardial infarction as established by typical changes in serial electrocardiograms. Their ages ranged from 43 to 74. It is important to note that three of these myocardial infarcts were clinically "silent"—not accompanied by relevant symptoms or physical signs. Other cases of gastrointestinal hemorrhage have been accompanied by typical angina pectoris, and in some of these the angina was the presenting complaint. Both the pain and the abnormalities of the EKG have disappeared following adequate transfusion of blood.

Discussion

These experiences have influenced us greatly in our management of gastrointestinal hemorrhage in elderly patients. We have come to realize that the pulse and blood pressure are not fully adequate guides to the necessary treatment, because the internal readjustments of the circulation tend to maintain normal vital signs, even at the expense

of renal and hepatic blood flow. For this reason we use, as crude reflections of the renal blood flow, daily measurements of urinary output and serial determinations of blood urea nitrogen. We judge the changing status of the hepatic circulation by serial estimations of serum bilirubin and of bromsulfalein retention. In certain cases blood volume, as determined by Evans blue dye (T-1824) or isotopic techniques, may give vital information about the adequacy of blood replacement. We would recommend a routine electrocardiogram on every elderly patient with severe hemorrhage, as some of the myocardial infarctions we have seen were painless.

The most important consideration in medical therapy is the full and prompt replacement of the blood lost. This must be adequate not only to relieve the signs of shock, but also to alleviate the dysfunctions of specific vital organs affected by ischemia. This is most critical in the patients with cardiac complications. Here, in addition to the repeated search for rales at the lung bases and other physical signs of increasing congestion, a most useful procedure is a series of venous pressure measurements, made possible by introducing a manometer into the transfusion tubing by way of a three-way stopcock. This permits nice adjustment of the rate of transfusion, maintaining adequate venous return to the heart, but avoiding congestion of the pulmonary vessels.

The decision regarding emergency surgery is one that requires a maximum of clinical judgment. One balances, of course, the risk of the operative procedure against the danger to the patient of continuing hemorrhage—the latter risk can be estimated not only from mortality statistics, but also in the case at hand from accumulating evidence of impending or actual injury to one of the vital organs. Hence, often these organ complications become indications for operative intervention rather than contraindications,—witness the case of our patient (Case 5) with the myocardial infarction. The prognosis for survival of the operation is often better than we think. Perhaps this is due to the previous development of collateral circulation in the heart and other organs, and of certain metabolic compensations such as an increased A-V oxygen difference. A heart or a kidney which has failed acutely because of blood loss and resulting anoxia would seem to have greater functional reserve capacity than one which has failed in the absence of such precipitating factors. Hence, if the functional status of the organ is rapidly restored to normal by transfusion, the operative risk should not be

considered as large as in the usual case of recent congestive heart failure or renal insufficiency. On the other hand, postponement of operation at the cost of continued ischemia of vital organs may lead to permanent damage of such degree as to increase the risk of corrective surgery at any future time. In this dilemma the risk of early surgical intervention usually seems the more awesome to the physician, but it is often the less dangerous to the patient.

Though we may comfort ourselves with the recovery of some of these patients from desperate states of illness, it would be better to prevent these crises insofar as possible. Prophylaxis in this field can be thought of in two steps. If an elderly patient is already bleeding from the gastrointestinal tract, it is well to remember that the consequences of this in terms of organ injury must pass first through a stage of reversible change before reaching an irreversible condition. Thus a patient may first experience angina pectoris before a worsening of his hemorrhage leads to a myocardial infarction. Clearly then, a patient with functional disturbances of a vital organ, who is not promptly responding to conservative measures, deserves full consideration for surgery before irreversible damage is produced.

The second step in prophylaxis is related to the treatment of the underlying gastrointestinal disease before hemorrhage occurs. This may require prolonged and painstaking medical control or carefully considered surgical correction, in the years before 50 when the consequences of hemorrhage are less severe. Our major opportunities lie in the better treatment of peptic ulcer, hiatus hernia and diverticulitis. Thus gastrointestinal hemorrhage in elderly patients is often a catastrophic consequence of long standing disease processes, which afford us ample time for preventive measures. In this respect, the proper consideration of geriatric disease in an individual must begin in his middle or even early adult life.

Summary

In elderly patients, gastrointestinal hemorrhage has a number of clinical consequences, which are related to the circulatory readjustments to a diminished blood volume. Compensatory reduction in renal or hepatic blood flow, if prolonged, may lead to acute renal or hepatic failure. Diminished blood flow in the extremities may result in arterial thrombosis and subsequent gangrene. With inadequacy of these com-

pensatory mechanisms, the coronary or cerebral blood flow is reduced, and, particularly in the presence of localized atherosclerotic narrowing, myocardial infarction or a cerebrovascular accident may occur. Cases are cited to illustrate each of these eventualities.

In such cases, the replacement of blood must be adequate to relieve not only hypotension but also the indications of renal, hepatic, and peripheral vasoconstriction. In some cases emergency surgery may incur less danger for the patient than would continued, inadequately compensated bleeding.

Gastrointestinal hemorrhage in the elderly is largely a preventable catastrophe, as most uncomplicated cases of chronic peptic ulcer, hiatus hernia, and diverticulitis can be safely and effectively treated in early or middle life.

REFERENCES

1. Welch, C. E., Allen, A. W. and Donaldson, G. A. Surgical management of massive acute upper gastrointestinal hemorrhage, *New Engl. J. Med. 252*:921-28, 1955.
2. Edholm, O. G. The effects of hemorrhage on the cardiovascular system in man, *Lectures on the scientific basis of medicine 1*:79-95, 1953.
3. Bearn, A. G., Billing, B., Edholm, O. G. and Sherlock, S. Hepatic blood flow and carbohydrate changes in man during fainting, *J. Physiol. 115*:442-55, 1951.
4. Schiff, L. Hematemesis and melena, in *Signs and symptoms* (C. M. MacBryde, editor), 2.ed., Philadelphia, J. B. Lippincott Co., 1952, pp. 330-333.
5. Gillman, J. and Gillman, T. Anoxia and the liver, with special reference to shock and chronic malnutrition, *Amer. J. digest. Dis. 16*:348-72, 1949.
6. Fazekas, J. F., Kleh, J. and Parrish, A. E. The influence of shock on cerebral hemodynamics and metabolism, *Amer. J. med. Sci. 229*:41-45, 1955.
7. Denny-Brown, D. The treatment of recurrent cerebrovascular symptoms and the question of "vasospasm," *Med. Clin. North Amer. 35*:1457-74, 1951.
8. Corday, E., Rothenberg, S. F. and Putnam, T. J. Cerebral vascular insufficiency, *A.M.A. Arch. Neurol. Psychiat. 69*:551-70, 1953.
9. Edwards, W. S., Reber, W. E., Siegel, A. and Bing, R. J. Coronary blood flow and myocardial oxygen consumption in hemorrhagic shock, *Surgical Forum* (Proceedings Clinical Congress of the American College of Surgeons) *4*:505-15, 1953.
10. Master, A. M. and others. Acute coronary insufficiency due to acute hemorrhage; an analysis of one hundred and three cases, *Circulation 1*:1302-17, 1950.
11. Dack, S., Corday, E. and Master, A. M. Heart in acute hemorrhage, *Amer. Heart J. 42*:161-83, 1951.
12. Scherf, D. and Klotz, S. D. Electrocardiographic changes after acute loss of blood, *Ann. intern. Med. 20*:438-52, 1944.
13. Kinney, T. D. and Mallory, G. K. Cardiac failure associated with acute anemia, *New Engl. J. Med. 232*:215-18, 1945.
14. Blumgart, H. L., Schlesinger, M. J. and Zoll, P. M. Multiple fresh coronary occlusions in patients with antecedent shock, *Arch. intern. Med. 68*:181-98, 1941.
15. Davis, H. A., Parlante, V. J. and Hallsted, A. M. Coronary thrombosis and insufficiency resulting from shock, *Arch. Surg. 62*:698-704, 1951.

THE ROMANTIC PERIOD IN MEDICINE

IAGO GALDSTON*

THE ROMANTIC PERIOD is generally treated like a pariah among the medical-historical episodes. By many it is considered to be an historical indiscretion which is better forgotten and forgiven, than brought up again and studied anew.

Garrison speaks of it as the period during which German medicine "drifted into a maze of incomprehensible jargon and fanciful distinctions as to the real and the ideal, identity, imponderables, polarities, irritability, metamorphosis, and the like." Castiglioni, who is generally the more urbane and cosmopolitan critic, epitomizes this period as one in which medicine "hurled itself into the adventure of transcendental hypotheses." But he argues that "In history, the study of errors is no less instructive than the study of successes."

I must admit that the study of "errors" entices me. Part of that enticement derives from a psychological and purely personal bias, i.e., a sympathy, or shall I say an empathy for the underdog. The rest of the enticement derives from the persuasion that many errors aren't errors at all, but are rather untimely truths, or if you will, truths for which men and the age are not at the given time quite ripe.

It were well to define the *Romantic Period* chronologically, geographically, and otherwise. But in doing so, we should recognize that the making of definitions is always arbitrary and generally somewhat misleading. Thus the philosophical derivations of the Romantic School are traced from Immanuel Kant through Fichte, Schelling, and Hegel, Schelling being the one who exercised the most immediate and the greater influence on medical thought.

Geographically, the nidus of Romantic Medicine is Germany, but its effects extended far beyond, and reached even to the distant shores of the United States. The essential characteristics of Romantic Medicine, unless given in negative and derogatory terms such as those used by Garrison and other critics, who find the period and the school most

* Executive Secretary, Committee on Medical Information, The New York Academy of Medicine.

antipathetic, can best be described in terms of their historical derivation and setting, for Romantic Medicine is best visualized as a movement, reactive to the antecedent developments in science and medicine.

Pat descriptions of the quintessence of Romantic Medicine in terms of "polarity," or "antithesis" are neither illuminating nor encompassing. It is true, as Ernest Hirschfeld has written: "*Die eigentliche Lebenslehre der Romantik aber war: Polarität.*" But as he promptly adds: "*Sie klingt uns überall entgegen, nicht nur in der Naturphilosophie.*"*

Polarity is a very ancient idea, encountered in the works of Heraclitus and Hippocrates. It is mirrored also in the apposites of the four humors. All of life, and all of experience attests to the external, rhythmic, cyclical return of the antithetical to that which Nietzsche termed "*Ewige Wiederkehr*", and which Freud has labelled the "repetition compulsion."

I am persuaded that the essential nature of the *Romantic Period*, and particularly of Romantic Medicine can be better grasped when viewed in the historical framework of its *advent*. Here Schelling's own words are most illuminating: "*Mit der Naturphilosophie beginnt, nach der blinden und ideenlosen Art der Naturforschung, die seit dem Verderb der Philosophie durch Bacon der Physik durch Boyle und Newton allgemein sich festgesetzt hat, eine höhere Erkenntnis der Natur: es bildet sich ein neues Organ der Anschauung und des Begreifens der Natur.*"**

According to Schelling, the Nestor of Nature Philosophy, what is wanted, is a reconstitution of *Naturforschung*, and a correction of those corrupting ideas and methods introduced by Bacon, Boyle, and Newton.

But what precisely are the corrupting ideas and methods which Schelling charges to Bacon, Boyle, and Newton? They are those of empiricism, wherein it is presumed that understanding derives from experience. Schelling, building on the philosophical ideas of his predecessors, Kant and Fichte, contends that it is the intellect which imparts meaning to experience–and not the reverse. This conviction is epitomized in Goethe's paradoxical and untranslatable dictum: "*Das Höchste*

* Hirschfeld, E. *Romantische Medizin. Zu einer künftigen Geschichte der naturphilosophischen Aera.* Leipzig, G. Thieme, 1930. ("The fundamental life doctrine of romanticism, however, was: polarity." "We encounter it everywhere, not only in Nature Philosophy.")

** Schelling's Werke II, cited by Hirschfeld, E., *op. cit.*, p. 70. ("With Nature Philosophy, which followed upon the blind and sterile ways of *Naturforschung* (exploration of nature) that had taken roots everywhere since the ruination of philosophy by Bacon, of physics by Boyle and Newton, there was inaugurated a deeper understanding of nature: there was created a new organ for the contemplation and understanding of nature.")

wäre: zu begreifen, dass alles Faktische schon Theorie ist." But Schelling dates his indictment rather late in the calendar of events. The corruption which he signalizes began some generations before, with the invention of printing in 1448, with the discovery of America in 1492, with the Reformation, 1517-1521, with the Paracelsian Chemotherapy of 1526, with the Copernican revolution in 1543, with the publication of the *Fabrica* by Vesalius on June 1 of the same year (1543), in a word with the constellation of events and developments which we name the Renaissance. (Bacon published his *Novum Organum* in 1620.)

The Renaissance is a period of somewhat mobile dating, but no matter how or when its termini are dated, this is one of its most distinctive achievements: when it was initiated, the universe was effectively compact and conceptually closed; at its expiration, and largely because of its disruptive and enlightening effects, the universe was no longer compact, nor was it any longer a "closed" universe.

The universe of St. Augustine and of Thomas Acquinas embraced the *alpha* and *omega* of all experiences and bound them together into a harmonious whole in the bonds of faith.* But the Age of Enlightenment, building upon the initiative of the Renaissance, discredited the simple faith of the believer, and proffered him a new faith, that of Science. "The philosophers of this time had left off contemplating the heaven of mediaeval piety, and were disposed to deify nature. They adored the rigidity of geometrical methods; they loved the study of the new physical science, which had begun with Galileo. Man they conceived of as a mechanism. Human emotions, even the loftiest, they delighted in explaining by very simple and fundamental natural passions. There is often something merciless and cynical about their analysis of many things sacred in human life. They are cold, formal, systematic, at least as to the outward shape of their doctrines."**

Descartes, profoundly representative of this age, began by doubting everything but his own existence, and sought to extricate himself from this murk of universal doubt and ignorance by the objective study of

* "This universe, made by God in six days, will not last forever. Just as it was created in time and as Adam and Eve were placed in the Garden of Eden, so it will proceed through all human history, in which the central events for the Christians were the Crucifixion and the Resurrection to the Last Judgment. Then all that was on the earth will be consumed by fire; the souls of the damned will be bound eternally in hell under the earth, and the souls of all the saved will be gathered in paradise; the spheres will stop revolving and the chief heavenly bodies will shine seven times more brightly. The whole marvellous mechanism of the universe will stand motionless forever as a monument to its creator. It was all a view of a universe that was closed, and it was all as clear and simple as the vast painted clocks run by machinery of which the men of the Renaissance were so fond. It was this universe that Copernicus upset in 1543." (Artz, F. B. *The mind of the Middle Ages.* New York, A. A. Knopf, 1953, p. 235.)

**Royce, J. *The spirit of modern philosophy.* Boston. Houghton. Mifflin Co., 1899, p. 28.

the data of experience. That was the inspiration and the technos of his *Méthode*.

It was this total and unsophisticated faith in the competence of objective experience to transilluminate and to reveal its own innate nature and meaning, that Schelling derogated and derided. The data of experience, he argued, do not of themselves fuse into meaningfulness. They do not indeed have an independent objective existence apart from the observer. But Schelling was not the first to propound this objection. Its most telling protagonist was the immortal Immanuel Kant of Koenigsberg (1724-1804). His *Critique of Pure Reason* appeared in 1781, and in the judgment of many learned men this work ranks with the highest creations of the human intellect.

It is impossible to summate Kant's *Critique* in brief, but this sentence drawn from the exposition of his philosophy by one who prized him affords a glimpse into his major thesis: "The understanding creates the laws of phenomenal nature, creates them, indeed, not without the most close and constant reference to the facts of sense, creates them, in truth, merely by actively uniting together these facts of sense, but still creates the whole organization, the coherence, the unity, the sanity, of our world of business, of society, and of science."*

I shall not undertake to expound the modifications, and the elaborations which Kantian thought underwent in the philosophies of Fichte, Schelling and Hegel. That would carry us too far in the realm of pure philosophy. I want rather to underscore the fact that *Naturphilosophie*, and also Romantic Medicine, are direct derivatives of the new humanism inspired by Kant's philosophy, a humanism that turned ever more from exclusive concern with the outer world, to the contemplation of the mind of man.

Before leaving this phase of my exposition I would make note that Kant also had his predecessors. Parallel to the intellectual movement of the Renaissance, with its particulate, analytical philosophers and scientists, there operated another movement whose protagonists included Paracelsus, van Helmont, Stahl, and Casper Friedrich Wolff: "Parallel with the philosophy of enlightenment, however, there developed another, entirely contrasted, conception of nature, precursors of which were Paracelsus and van Helmont, and which, possessing in Stahl, Swedenborg, and Caspar Friedrich Wolff its scientifically most im-

* Royce, J. *op. cit.*, p. 131.

portant representatives, appears throughout the eighteenth century under various forms, a view of life which sees in natural phenomena an expression for the operations of spiritual powers, whereas, according to its tenets, the mechanical explanation of nature admits of only a superficial observation of what takes place, without any insight into that inherent connexion in existence which the spiritual powers imply. This attempt to regard nature as a living entity, to look for connexions in phenomena where, when viewed superficially, none are apparent, has constituted this tendency's greatest service, besides which the freedom of mechanical principles in many cases, admitted of greater liberty in the interpretation of special phenomena, as Wolff's embryological and Sprengel's botanical investigations proved. The weakness of this spiritualistic view of nature has lain in the frequent desire to solve by mystical formulae, problems the solution of which would have required observation and deep thought."* This movement has been described as a phase of the oft recurring Neo Platonism.** In essence it seeks to propound the vision of Nature as a living whole, and to search for the interconnection of its manifold phenomena, finding in each, meaning and significance which transcends the limited and the patent, and tracing its derivation from sources remote to its immediacy.

But to revert to Kant: we need to recognize that he, no less, and I would say more significantly than Descartes, helped to initiate the modern science of psychology. Goethe had phrased the apt couplet, so descriptive of Renaissance science:

"Mein Kind ich habe es klug gemacht
"Ich habe nie über das Denken gedacht"

Kant, however, did precisely the opposite–*Er hat über das Denken gedacht*–and he thus gave new meaning to "subjectivism" in psychology, that is to the study of those mental phenomena which cannot be reduced to brain or body processes.*** Ultimately, however, Kant's critical study of the cognitive process led to much more than "subjectivism" in psychology, important though that was. It inspired and directed the modern study of epistomology. It made the "meaning of meaning" not only a legitimate but a fundamental inquiry, prerequisite to the stabilization of scientific data and functions.

*Nordenskjöld, E. *The history of biology. A survey;* translated from the Swedish by L. B. Eyre. New York, A. A. Knopf, 1928, p. 269.
**Moon, R. O. *The relation of medicine to philosophy.* London, Longmans, Green & Co., 1909.
***Boring, E. G. German psychology before 1850; Kant, Herbert and Lotze, in his *A history of experimental psychology,* 2 ed., New York, Appleton-Century-Crofts, 1950, chap. 13, pp. 246-272.

You will find this derivative of Kantian philosophy broadly treated in Ernst Cassirer's *An Essay on Man,* and in greater and more particular detail in his *Substance and Function.* But I perceive that in pursuing the origins of Romantic Medicine back to its philosophic roots, we have been carried far too far from the core of our concern—namely—what in effect happened in medicine during these years. To these considerations we will now turn our attention.

The ancient physician, we need recall, considered himself to be the servitor of Nature, and his art as ancillary to the healing powers of Nature. It was the healing power of Nature, *the vis medicatrix naturae,* that brought the sick man back to health. The services of the physician were not deemed negligible or irrelevant; you will recall how highly Nestor was esteemed in the Homeric Saga. But the prevailing belief was that where Nature would not prevail, neither the physician's arts nor his skills could avail. Indeed you will find Hippocrates counselling the physician not to undertake the treatment of the "incurable" disease. This counsel, incidentally, has been variously interpreted and more often than not to the discredit of Hippocrates and his followers. But I think such derogatory interpretations are unwarranted, and are made without regard to the over-all philosophical and humanistic position of the Hippocratic physician.*

Ancient Greek Medicine, we need recall, through the regency of Galen's teachings, held sway over the medicine of Europe and of the Islamic lands, for almost two thousand years. "It can be safely said that up to the end of the 18th century, Galen was the medical author who was most frequently consulted and the only one to be placed on a level with Hippocrates."** It will profit us then to look more closely at the Hippocratic-Galenic system. It too was like the universe of the medieval philosopher, a closed system. Galen is said to have anticipated all the questions and to have been ready with an answer to each.

Man was a component, an immensely important one, in the scheme of the universe, and his being was presided over by Nature with whose benign powers the wise physician aligned both his arts and his skills. In the realm and during the period of Christian sovereignty, God took

* Hippocrates had, so to say, his early critics as well. The Methodist Asclepiades of Bythinia characterized Hippocratic Medicine as a meditation of death. In effect, however, this criticism was little justified, for the Hippocratic physician was an active therapist, well informed in the uses of many drugs. Yet his scheme of treatment was primarily physiological in the sense of corrective regimen; and for therapy he depended chiefly on the proper diet, fresh air, purgations, barley water, wine, massage, emetics, and hydrotherapy. The Hippocratic physician was also an excellent surgeon.

**Castiglioni, A. *A history of medicine.* New York, A. A. Knopf, 1947.

over from Nature, and it was God's laws that guided the physician's practices. In the famous saying of Paré—it was God who did the healing while Paré merely served both God and the wounded man, by bandaging the latter. Though medicine was buttressed with much specific knowledge, anatomical, pharmaceutical, and therapeutic, it was, all in all, rather simple in its basic schemes. Etiology was reduced to elementary dyscrasias, and nosography was general and symptomatic rather than particular. The patient had a rheum, a flux, a catarrh, an obstipation, a sweat, a fever and so on. Therapy was dictated, in the main, by the presenting symptoms, by the etiological analysis (i.e., the nature) of the dyscrasia postulated, and also be it added, by the general constitution and appearance of the patient.

The basic fact then is that the physician oriented in the Galenic tradition had much to learn, but he could and did feel secure in his knowledge and in the conceptual scheme upon which his practice rested. It was a complete scheme, a closed system, and, it too was shaken and shattered by the advent of modern science.

Paracelsus (1493-1541), paradoxical as it may seem, was among the first to breach the strongholds of ancient medicine. He not only burned the works of Galen and Avicenna (that is according to tradition—Sudhoff denies it) but more significantly, he challenged the effectiveness of the Galenic simples, substituted for them quintessential tinctures and distillates, and introduced alchemical elements such as mercury, lead, sulphur, iron, arsenic, copper sulphate, and potassium sulphate into medicinal use. Far more effective in the tearing down of ancient, that is of Galenic medicine, was the anatomist Andreas Vesalius. Not only did *De Fabrica Humani Corporis* (1543) show up the faults and errors of Galenic anatomy, but it provided the essential basis, the foundation, for the objective study of medicine in all its manifold divisions. Harvey, in his epoch making work, not only initiated the modern study of physiology, but demonstrated more effectively than ever Bacon did in his sonorous expositions, the fruitfulness of the inductive method.

Paracelsus, Vesalius and Harvey were medical critics and initiators, but medicine itself was not immune to the effects of the philosophical innovations of Bacon and Descartes, nor was medicine unaffected by the new scientific discoveries of Copernicus and Galileo. Indeed, medicine took on the complexion of the prevailing age, and in medicine too, it came to be thought that all bodily processes took place in accordance

with the known laws of physics and chemistry. Two schools of thought issued therefrom—the iatro-chemical and the iatro-mechanical. The leader of the first was Sylvius (Franz de la Boe—1614-1672), professor of Leyden. The founder of the iatro-physical, or as it was also termed the iatro-mechanical school was Giovanni Alfonso Borelli (1608-1679). Both schools soon gained many adherents. Since chemistry was then still an undeveloped science, the iatro-chemical school of medicine soon became entangled in many finespun speculations. The iatro-physicists, on the other hand, achieved some clear insights into the fine mechanical and structural operations of the body. Yet neither school proved satisfactory in guiding and sustaining the physician in his efforts to comprehend health and disease, and in his endeavor to bring the ailing individual back to health.

Physicians of great stature and generous endowments, men like Sydenham (1624-1689) and Boerhaave, cast all schools and systems aside and reverted to the Hippocratic vision of man and the universe, and to the methodic-empirical practice of medicine. Sydenham has been termed the English Hippocrates. Boerhaave (1668-1738) instituted the modern system of clinical, that is bedside, teaching and because so many students from all parts of Europe came to study with him at the University of Leyden, he was titled "*communis Europae praeceptor*." But neither Sydenham nor Boerhaave could stem the tide of speculative theorizing, nor effect a return to the simple yet embracive methods of Hippocratic study and observation. The result was "chaos and a babble of tongues."

Garrison describes 18th Century medicine as "dull and sober sided." I find it rather exciting even though largely futile and misguided. No age as much at loose ends could prove anything but exciting. And at loose ends it was—for medicine had been torn from its ancient moorings, and had not yet come into the snug harbor of modern biological knowledge and thought.

It is not my intention to detail the confusion of 18th Century medicine, nor in the space available, attempt to "draw order out of chaos." However, we do need to appreciate that there *is* a rationale to the anarchy in medical thought that prevailed in that period. It is the rationale of the transition state. In it we witness the travail of a scanning process carried out in gigantic dimensions; a scanning process seeking to re-establish social, cultural, economic, and ideological equilibrium on a plane different from, and on a scale grander than, that which had

been disturbed and disrupted in the wake of the Renaissance and by the advent of modern science. In these respects, our own century has much in common with the 18th Century.

Medicine is both a science and a discipline. But its ultimate rationale lies in the pleading needs of the sick, in the mute supplications of the feverish child, in the anguish of the woman in labor, in the tortuous struggles of the strong man writhing in pain. These are time-and-occasion-bound instances, wherein the physician is exposed to crucial testing. We fail or we succeed, and the issue is of mortal consequence to the sick. Celsus, the great Roman medical historian, encyclopedist, and commentator, who though vastly learned was not a physician, spoke for all suffering humanity when he said: "*Non interesse quid morborum faciat, sed quo toleat.*" Translated freely and in the suffering impatience of the sick one, this means "a plague on all your theories and speculations as to the cause of this illness—hasten to rid me of it."

It is in these respects that the *Scientia Nuova*, particularly in the field of medicine, proved so grievously disappointing. Physician and patient alike lamented and bewailed the impotence of medicine. Two significant texts reflect the frustration of this period—Johann Georg Zimmermann's two volume work *Von der Erfahrung in der Arzneykunst*, and Cabanis' work with the title *Du Degré de Certitude de la Médecine*. Zimmermann's work, which carried as its motto, the quotation from Bacon—"*non ex vulgi opinione, sed ex sano judicio*"—was a challenge to medicine to become scientific. "*Der beobachtende Arzt hört die Natur, der experimentelle frägt sie aus.*" The second, that by Cabanis, is apologetic in character. The "*certitude*" of medicine, Cabanis argued, could be only practical and "*il faut s'en contenter.*" The total effect of these exhortations and inquiries concerning the scientific validity of medicine, appears to have been akin to that resulting when the centipede was asked which foot he puts forth first—that is, utter confusion.

Desperate confusion, as I have already indicated, reigned chiefly in the realm of therapy. Etiology and nosography were also in a rather confused and bewildered state. The only branch of medical science which appeared to be quite well founded and assured was pathological anatomy. Morgagni initiated this discipline in the publication of his classical work *De Causis et Sedibus Morborum*. John Hunter in England, and Bichat in France advanced the study of pathological anatomy

and made of it, in effect, the foundation basis of the *science* of medicine, and the presumptive rationale of therapy. For having, as it was presumed, set out and defined the "*causis et sedibus morborum*", the cause and site of disease, it was further assumed, with seemingly irrefutable warrant, that the merit of a therapeutic process or agent could be assessed by observing, and by mathematically defining its effects on the morbid locus and process. This assumption gave rise to the *Statistique Médicale* of Louis and of Cavaret. All of this was very interesting and indeed inspiring, but it had little to offer the practicing physician and his patient.

The French medical historian, P. V. Renouard, published a series of *Philosophical Letters on Medicine in the 19th Century*. In the first of these letters he set forth the proposition that "the bitterest criticisms which have ever been made upon medical science, and upon those who cultivate it, have flown from the pens of physicians" (p. 599). And to prove his point he cites the opinions and judgments of a number of the outstanding 19th Century medical scientists. Thus Bichat described the *Materia Medica*, historically, and of the period, as "an incoherent assemblage of incoherent opinions . . . a shapeless conglomerate of inexact ideas, of observations often puerile, of illusory remedies, and of formulas as oddly conceived as fastidiously arranged." "It is said," Bichat wrote further, "that the practice of medicine is repulsive. I say more than this: it is, in respect to its principles, taken from most of our *Materia Medicas*, impracticable for a sensible man." Broussais, who as our historian (Renouard) observes, was nurtured in the physiological ideas of Bichat, and the philosophy of Condillac and Cabanis, had no kindlier words for his fellow practitioners, nor a higher regard for the science of medicine—save only, of course, for his own system. "Imagine," Broussais exhorts his readers, "in all parts of the civilized world, legions of physicians who do not even suspect the existence of gastric inflammation [that was Broussais' theory] nor the influence which this phlegmasia exercises upon the other organs; see them pouring floods of vomits, purgatives, heating remedies as wine and alcohol, liquors impregnated with bituminous substances and with phosphorus . . . contemplate the consequences of this medical torture, the agitation, trembling convulsions, and phrenitic delirium, the cries of pain, tortured expression of face, and the burning breath of all these unfortunate ones. . . ." and so on, in the same vein, winding up in the peroration:

"What I have given suffices to prove that the epigrams of philosophers and poets, upon the faults of physicians and the pernicious effects of their art, are but feeble sketches by the side of this picture, at once so animated and so frightful."*

To these were added many other voices, condemning, disparaging, criticizing each and every aspect of medical science and medical practice. The cynical spirit of this period is well summated in the aphorism of M. Bouillaud *(Essai sur la Philosophie Médicale):* "Medicine should, to a certain point, be assimilated to the science of those Augurs who could not look each other in the face without laughing."

In summating the state of medicine in the first half of the 19th Century, Renouard wrote: "This want of union . . . does not relate to detail only; no, it is mostly upon the very principles which form the foundation of medical science that they disagree. Each one of these medical legislators aspires to nothing less than to build his ideal monument upon the ruins of all others. They all commence by destroying what exists, leaving to others to build up again when and how they can" (p. 604).

This state of affairs yielded two resultants; a plethora of systems, and Therapeutic Nihilism. Of systems there was seemingly no end. Doctors termed themselves allopaths, homeopaths, isopaths, physiopaths, eclectics, botanics, and so on. Therapeutic Nihilism was, so to say, the negation of all schools and systems. Therapeutic Nihilism is invariably referred to the so-called New Viennese School. Its foremost proponents were Rokitansky, Skoda, and Dietl. Rokitansky was the author of the celebrated *Handbuch der Pathologischen Anatomie*, published in 1842-46. He held pathological anatomy to be the touchstone of therapy, but he embraced also patho-physiology, the latter conceptualized in terms of chemical factors. Skoda is primarily famed for his extensive and refined studies in physical diagnoses—notably auscultation—initiated by Laennec, the inventor of the stethoscope, circa 1818. His rigorous and methodical assessment of all medical theories and practices inevitably led him to look upon the prevailing therapies with abysmal skepticism. Skoda was reputed to have reduced the number of his medicamenta to *Aqua Laurocerasi* (Cherry Laurel Water).

The most effective proponent of Therapeutic Nihilism and one who at the same time once again celebrated Nature's healing powers, was

* Broussais, F. J. V. *Examen des doctrines médicales et des systèmes de nosologie.* Paris, Mequignon-Marvis, 1821, p. 601.

Dietl (1804-1878). In 1845 he published a series of essays in the *Zeitschrift der Gesellschaft der Aerzte zu Wien*, in which he at one and the same time derogated the therapies of the past and boldly sketched those of the future, founded, as he envisioned them, on a thoroughly rational basis. This rationality not only embraced, but was founded on, the *vis medicatrix naturae*. "*Nur die Natur kann heilen.*"

In an eloquent passage he inquires why it is that the astronomer is not required to change day into night, nor the physicist, winter cold into summer heat, nor the chemist, water into wine. Yet the physician is called on to cure lung disorders *(Lungensuchten)*, hydropsies, gout, heart failure, and so on. Is it because the physician's knowledge or his science warrants such expectations? Not at all! That "only nature can heal," Dietl wrote, is the highest and the most fundamental principle in practical (clinical–i.e., *praktischen)* medicine, and one to which we will needs adhere, even when we will have discovered some new subordinate "*Heilprinzip.*" It was in this meaning context and not in the spirit of callous indifference that Dietl wrote (1851): "The physician must be judged according to the amount of his knowledge, and not according to the results of his cures; it is the investigator, but not the healer, that is to be appreciated in the physician." *("In Wissen und nicht in Handeln liegt daher unsere Kraft!"*)* This must, for now, suffice as a background for our particular concern with Romantic Medicine. You appreciate, of course, that I regard the full stretch of this period, the 18th no less than the early part of the 19th Century as having been romantic in its expectations and its orientations. In my meaning, "romantic" is a rather inclusive term. Descartes and Bacon were to my mind romantics in the unrealistic expectations of their respective systems. But that's an issue apart.

Let us return to Romantic Medicine. As we had observed, with the advent of modern science, medicine was split into two divergent schools of thought, the iatro-mechanical, or iatro-physical, and the iatro-chemical. There were other so-called diversionist schools–the animist or vitalist school, for example. But these we will largely disregard, for the sake of clearer orientation. This I grant is arbitrary, and even more arbitrary are some of the generalizations which I will shortly present. But the arbitrariness lies in the elimination of peripheral items and not in the corruption or distortion of the basic or core data. Thus one such

* Petersen, W. F. *Hippocratic wisdom.* Springfield, Ill., C. C. Thomas, 1946, p. 200.

arbitrary but valid generalization is that iatro-physical medicine prospered in France, while iatro-chemical medicine found favor with the English. Yet there were partisans of both schools in all lands. The generalization then rests on preponderance rather than on universality. Germany also had adherents of both schools. But German medicine was effectively influenced by neither. It was influenced by the thoughts and teachings of Schelling and of his elaborators. Among Schelling's medical disciples and exponentialists, the more noteworthy were Lorenz Oken (1779-1851), Ignaz Döllinger (1770-1844), Philipp Franz von Walther (1782-1849), and Kielmeyer (1765-1844). To these disciples of Schelling, science is, according to Haeser, indebted for contributions of abiding worth, and for inspirations of the most significant order, which, to quote Haeser—"have even in their errors yielded much of value."*

Oken is the most romantic character in this group of disciples. The son of a peasant born in a small village near Offenbach, he aspired in his youth to become, first a soldier, and later a mathematician. In 1800, when 21 years of age, he was drawn to the study of medicine. Two years later, he espoused Schelling's nature philosophy in protest against the "uninspired sensualism" of the British and French philosophers. In romantic effusion he compounded, as he himself professed, the teachings of Democritus', Aristotle's, and Goethe's ideas on the Reality of the Absolute, Schelling's concept of the Idea, and Hegel's Logos, into mathematic-symbolic-graphic representations *(mathematisch-symbolisch-bildhafte Gestalten)*. Oken was a phenomenal, an inspired, and a most fertile personality. He founded and edited a journal with the title *Isis*. In the last issue of this publication, he sketched the concept of evolution. As a biologist and a comparative anatomist, Oken sought to bind the world-entire into an organic whole, complete as is the figure zero—which he held to be the Infinite, the resultant of the embrace of positive and negative. Oken envisaged the existence of primal and undifferentiated cells from which he derived, in theory of course, all forms of living organisms. He is thus, with warrant, credited with having anticipated the cellular theory. Ignaz Döllinger, who was professor at Würzberg and at München, shared with Oken, a deep interest in the developmental history of man, but Döllinger is more noted for

* ("*Diesen Schülern Schellings verdanken die Naturwissenschaften Arbeiten des bleibenden Werthes, Anregungen der bedeutendsten Art, die selbst durch ihre Irrthümer manchen Nutzen gebracht haben.*") Haeser, H. *Lehrbuch der Geschichte der Medicin.* Jena, F. Mauke, 1853, p. 810.

his application of the microscope in the study of both anatomy and physiology.

The early protagonists of Schelling's *Naturphilosophie* were essentially academic. In clinical medicine, Schelling's ideas were propounded and advanced by a host of influential practitioners and resourceful clinicians. Among these are counted Roschlaub, Marcus, Troxler, Kilian, Kieser, Malfatti, and J. Ad. Schmidt. These were the authors of numerous texts and monographs dealing with medicine conceived in the framework of Schelling's *Naturphilosophie*. Their joint products form the essential Corpus of Romantic Medicine. We may, at this point, properly inquire, what was the inspiration of this Corpus? What did it teach? And more specifically, how did the adherents of Romantic Medicine practice medicine? Bluntly, it can be said, using a term of recent genesis, that the inspiration of the Corpus of Romantic Medicine was ecological in character. Whereas the Galilean-Baconian-Cartesian science dismembered the universe into its ever more fine and finer components, and sought to study them in "splendid isolation," hoping thereby and thereafter to achieve a comprehension of the whole in the fusion of the particular knowledge–Romantic Medicine, quite in the spirit of the modern Gestalt psychology, held that the part did not attain to its ultimate meaning save in relation to the whole, the whole being greater than the mere sum of its parts. In this belief, disease was viewed not as an experiential interloper in the realm of normal being, but rather as a phase of being, relative to health. Disease was deemed to be meaningful and it was up to the physician to fathom its meaning. All phases of the living process engaged the interest of Romantic Medicine, among them notably sleep and the dream. In the writings of Schelling and Novalis are to be found some very provocative observations on the functions of the dream. Novalis, for example, spoke of dreams as "excrements of the brain." Gotthilf Heinrich Schubert (1780-1860) composed a work on dreams which in many respects anticipates Freud's dream theories. Carl Gustave Carus, who is to be counted among the Romantics, wrote his now famous *Psyche*. This work begins with the pronouncement: "The key to the comprehension of the nature of conscious psychological experience lies in the region of the Unconscious." Carus was an intimate friend of Goethe. The Romantics were deeply interested in psychiatry and in psychotherapy. They strove to penetrate into, and to comprehend insanity. Justinus Kerner in Weins-

berg housed a number of emotionally sick persons in his own home in order that he might observe them more closely. "*Die romantische Art der Krankenpflege war beinahe Gottesdienst geworden*," wrote Leibbrand.* But in other respects Romantic therapy, qua therapy, was not distinguished for its rationality or effectiveness. "*Der romantische Arzt in der Praxis, das ist das kärglichste Kapitel in der Geschichte der romantischen Medizin.*"** Therapy was directed by the Brownonian system of sthenia and asthenia. The principle of the contraries, as well as the homeopathic principle of similarities guided therapy discretely. Thus asthenia was treated with stimulants; sthenia with sedation. But frozen limbs were thawed with cold water! Mesmerism had its numerous practitioners among the Romantics. Yet it should not be overlooked that hygiene and regimen were important components of Romantic therapy. Diet, fresh air, massage, exercise, balneotherapy, were employed in the treatment of the sick. Withal the therapeutic scene is not inspiring. It is, however, more pleasing than that to be witnessed, say in France, where under Magendie's instruction physicians were feeding their helpless victims massive doses of alkaloid poisons, where Jean Baptiste Bouillaud (1796-1881) was exsanguinating them, and where Broussais poured upon them "buckets of leeches."***

Homeopathy did not command the respect of the critical because of Hahnemann's speculations on pharmacodynamics, but statistical evidence did show that pneumonia sufferers treated in Vienna's homeopathic hospital stood a better chance of recovering than those treated in the allopathic hospitals, in which blood-letting was a common practice.**** I would not, however, give you the impression that Romantic Medicine was everywhere and at all times illuminated with a transcending rationality. I am persuaded that in many respects it was inspired, but there is no doubt that in numerous instances it was wild in its speculations, and even silly in its analogies.

Thus one of its adherents compared the red blood cell to the earth with its opposite polarities and electric potentials. Another accounted for an epidemic of typhus in terms of a coction of the universe.

Some of the medical historians make a Roman holiday of these speculative indiscretions of Romantic Medicine. It affords them great

* Leibbrand, W. *Romantische Medicin*. Hamburg, H. Goverts, 1937, p. 82.
** Leibbrand, W., *op. cit.* p. 181.
*** Petersen, W. F. *op cit.* p. 284. (In 1833, 41,500,000 leeches were imported into France.)
**** Petersen, W. F. *op. cit.*, p. 189.

sport to cite the wild spinnings of the Romanticists. To such historians I would cite that superb injunction to humility: "First cast out the beam out of thine own eye; and then shalt thou see clearly to cast out the mote out of thy brother's eye."

In the last analysis, these were innocuous speculations. Against them can be arrayed an infinite number of "experimental ventures" which were not at all innocuous in their effects. No generation of scientists, no age of probers-into-the-unknown is ever exempt from error. No generation of men is infallible in its speculations.

Romantic Medicine came to an end neither with a whimper nor with a bang. It just evanesced. In the second half of the 19th Century, medicine "turned modern." Virchow, Claude Bernard, Pasteur, Robert Koch, et al., are names which are well known, and there would be no point in dwelling upon their accomplishments. Only one issue remains to be treated, and that is: What is the warrant for any interest in Romantic Medicine? Are not those historians correct who dismiss this episode as a *Walpurgisnacht* nightmare?

Quite evidently, I do not share in this opinion. On the contrary, I feel that this is a period charged with infinite inspirations, and that its thinking and its speculations are more meaningful today than they were in their so-called heyday, a century ago. So many of their intuitive ideas, scoffed by the cock-certain science of the late 19th Century, have become realities in our day. Schelling's dictum: "*Die höchste Vervollkommnung der Naturwissenschaften wäre daher die vollkommene Vergeistigung aller Naturgesetze zu Gesetzen des Anschauens und Denkens. Die Phaenomene müssen völlig verschwinden, und nur die Gesetze (das Formelle) bleiben.—Die vollendete Theorie der Natur würde diejenige seyn, kraft welcher die ganze Natur sich in Intelligenz auflöste*,"* has been substantially realized in Einstein's theory of relativity, lately elaborated anew. The Romantics' speculations, as to polarity, and many other seemingly foolish ideations and analogies, are solid components of today's scientific theory and technique. But that which appeals to me most in Romantic Medicine is the ecologic idea, the recognition which the Romantics shared in common, of the linkage of man to the universe and of the universe to man. We are today beginning to

* Schelling, F. W. J. *System des transcendentalen Idealismus.* Tübingen, 1800. ("The highest perfection of the natural sciences, . . . would be a complete intellectualization of all natural laws, into the laws of observation and of thinking. The isolated phenomena must disappear completely, and only laws (the formal one) must remain.—The most perfect theory of nature would be the one which causes all nature to dissolve into intelligence.")

appreciate how very narrow and, in many respects, how shallow were and are, the specifists' ideas which the physicians in the last century and in the first quarter of this century, shared in common. This, I submit, warrants our sympathetic study and our respectful review of what the Romantics in medicine thought, believed and felt. I heartily subscribe to Haeser's judicious assessment of the significance of the Romantic School: "The contemporary world which finds its preoccupation with the singular and the perceptible so compelling, is, therefore, disinclined and indeed, incompetent to comprehend or to appreciate all this and much more besides. A more tranquil and less prejudiced generation, inclined as well to observe as to contemplate will, perhaps, recognize that there is many a precious nugget of pure gold to be found in the best of the *Naturphilosophie* writings which may eventually prove rewarding in diverse and unexpected ways."*

* Haeser, H., *op. cit.*, p. 816. (*"Mag deshalb die Gegenwart, welche in der Beschäftigung mit dem Einzelnsten und unmittelbar sich Darbietendem ihre Aufgabe findet, dies Alles und noch Anderes anzuerkennen weder geneigt noch befähigt seyn,—ein ruhigeres und unbefangeneres Geschlecht, das eben so sehr zu beobachten, als zu denken gesonnen ist, wird vielleicht erkennen, dass die tüchtigsten Schriften der naturphilosophischen Literatur noch manches Korn gediegenen Goldes führen, dem reiche Zinsen zu tragen dereinst vielleicht beschieden ist."*)

MANAGEMENT OF PANCREATITIS: ACUTE AND CHRONIC

*Transcription of a Panel Meeting on Therapeutics**

CHARLES F. WILKINSON, JR. . . . Moderator

Professor and Chairman, Department of Medicine, New York University Post-Graduate Medical School; Director, Department of Medicine, University Hospital and Fourth Medical (N.Y.U.) Division, Bellevue Hospital

Panel Members

J. WILLIAM HINTON

Professor and Chairman, Department of Surgery, New York University Post-Graduate Medical School; Director of Surgery, University Hospital and Fourth Surgical (N.Y.U.) Division, Bellevue Hospital

MICHAEL LAKE

Assistant Professor of Clinical Medicine, Cornell University Medical College; Assistant Attending Physician, The New York Hospital

MILTON R. PORTER

Associate Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgeon, The Presbyterian Hospital

* Presented at the Monthly Panel Meeting (Third Series), at The New York Academy of Medicine.

MODERATOR CHARLES F. WILKINSON, JR.: With almost any condition, I think it important to establish first the etiology of that condition.

Accordingly, I would like to ask Dr. Lake what he feels are some of the etiological factors in acute pancreatitis.

DR. MICHAEL LAKE: About half of the cases of acute pancreatitis are associated with biliary tract disease and a large percentage of cases occur in alcoholics. Acute pancreatitis can develop from traumatic injury to the abdomen, either penetrating or crushing. The immediate precipitating cause is often a large meal or an alcoholic spree. I know of no other causes except sudden interference with circulation such as an embolus or thrombus which cuts off the blood supply to the pancreas. However, there are a great many cases in which no etiological factor can be determined.

MODERATOR WILKINSON: *Dr. Porter, have you any comments to make on this?*

DR. MILTON R. PORTER: I think two factors might be mentioned. One is the psychic factor. However their effects are mediated,—whether through spasm of the ampulla or spasm of the ducts or vessels,—we feel sure psychic factors do play a role in pancreatitis. We have one patient who gets acute pancreatitis every time she argues or fights with her husband. It can be predicted that when she has a quarrel she will then come in with a pain in the abdomen half an hour or an hour later. We will find the amylase high and symptoms of pancreatitis. Although not often, we also see pancreatitis as a complication of gastrectomy for ulcer or cancer. In the course of that operation we may not realize that we have touched the pancreas, but apparently we have damaged it or done something to it without cutting into it. This is a recognized complication of gastrectomy.

MODERATOR WILKINSON: *Dr. Hinton, do you have any idea why complications of gastrectomy persist? I believe you have been interested in that problem in recent years.*

DR. J. WILLIAM HINTON: From our observations it is a rare complication of upper abdominal surgery. First, I would like to say that in our experience the diagnosis of acute or chronic pancreatitis is most difficult. We have run serum amylase tests on 100 patients, 71 of whom had had upper abdominal or intra-abdominal surgery, most of them upper biliary tract surgery or gastrectomies. The results are so varied that it is difficult to intelligently interpret the serum amylase determina-

tions. In our series those who had high serum amylase findings had few, if any, complaints referable to their abdomens and in the 29 patients with extra-abdominal surgery, four had high serum amylase determinations. Our experience leads me to believe that a serum amylase determination per se is, at least in our hands, of little value in establishing the diagnosis of acute pancreatitis.

MODERATOR WILKINSON: I would rather wait till a little later to go into the diagnostic procedures but I would like to say at this point that we have seen the so-called postgastrectomy syndrome, where the predominant features were loss of weight, negative nitrogen balance and general inanition. Many of these patients have responded to the regimen which we would ordinarily use to treat the patient with chronic pancreatitis. I still think that the mechanism of this pancreatic deficiency following gastrectomy is probably in doubt. *Would the panel as a whole agree or not agree with that?*

DR. PORTER: It is in doubt. I think there are a few factors which we probably can guess at, such as not having the food go through the duodenum.

MODERATOR WILKINSON: *You think that there is a mechanical factor then, that might lead to understimulation of the pancreas?*

DR. PORTER: Yes, I think that could be a factor. That is one of the arguments proposed by those who feel that the Billroth-I hookup is better than the Billroth-II. They feel that fat absorption is better afterwards and one would have to assume that it might be due to the fact that the pancreas is better stimulated.

MODERATOR WILKINSON: *What is your opinion, Dr. Lake?*

DR. LAKE: I don't have any very fixed opinion on the subject, Mr. Chairman, because bile acid stimulates secretin formation just as much as hydrochloric acid.

MODERATOR WILKINSON: *If the food does not pass through the free part of the duodenum, do you have as much flow of the bile acid as if it passed through the duodenum?*

DR. LAKE: Perhaps not.

MODERATOR WILKINSON: *The next question I would like to propose to the panel is: What is the relationship between acute pancreatitis and chronic pancreatitis? Dr. Porter!*

DR. PORTER: I am not sure that I understand your question. Do you mean what per cent of people have acute pancreatitis and then go on

to have other attacks or to a chronic stage?

MODERATOR WILKINSON: *In acute pancreatitis we have a fairly clear-cut clinical picture, and it may recur many times, and then chronic pancreatitis develops. Do you think that this is usual or do you think this is unusual?*

DR. PORTER: I have no data on it. I could only give you an impression.

MODERATOR WILKINSON: *Will you give us that?*

DR. PORTER: I think it is not as high a percentage as I would expect. I would guess perhaps 15 per cent.

MODERATOR WILKINSON: Dr. Lake?

DR. LAKE: At the Mayo Clinic the group had some information on that and I think they thought not more than 7 to 15 per cent of the people with an initial attack of acute pancreatitis developed other attacks. Also, quite a few people developed chronic pancreatitis without any history of really acute pancreatitis.

MODERATOR WILKINSON: *Dr. Hinton?*

DR. HINTON: I think one should try to differentiate between the two forms of the disease called acute pancreatitis. One (and the most common), is the edema of the pancreas which is generally called acute pancreatitis. The other is the hemorrhagic type of pancreatitis which constitutes by far the smaller percentage, maybe 15 per cent of the cases of acute pancreatitis. My remarks are confined to the acute hemorrhagic form of pancreatitis. Fifty per cent of those with this type die regardless of how treated,—medically or surgically. So 50 per cent of the cases are eliminated before you start. What happens to the other 50 per cent I do not know, but I agree with Dr. Lake—of those cases of chronic pancreatitis that I have seen I can recall none that ever had attacks of real acute hemorrhagic pancreatitis.

MODERATOR WILKINSON: *Dr. Lake, I think that you were probably the first person in this area, if not in this country, to use the secretin test. Would you care to begin the discussion on the diagnostic criteria for acute pancreatitis?*

DR. LAKE: Dr. Joseph Diamond first used the purified secretin in this country. I don't think the secretin test is applicable often to the case of acute pancreatitis because the patient is vomiting and sick and not anxious to swallow a tube and keep it in for a couple of hours. I think it is more applicable to cases of chronic pancreatitis.

MODERATOR WILKINSON: *We have ruled out one test for acute pancreatitis! What test do you like best?*

DR. LAKE: In spite of Dr. Hinton's experience, the serum amylase and lipase determinations are probably the only laboratory tests which are of value in acute pancreatitis. False positives do occur. You may get increased levels with intestinal obstruction. You may get an increase with perforated ulcer and you may get an increase after morphine with spasm. But should you get an increase of as much as 400 or 500 units, and if you can rule out perforated ulcer, I think the determinations are of value.

MODERATOR WILKINSON: *You may also get an increase after codeine, is that not correct?*

DR. LAKE: Yes, you can get an increase after codeine but I don't think you usually get increases of that magnitude after the drugs.

MODERATOR WILKINSON: *Do you still believe that when the patient has symptoms of acute pancreatitis it would be better to use a drug such as Demerol, instead of morphine or codeine, until you have done the test?*

DR. LAKE: Yes, I think it would.

MODERATOR WILKINSON: That is a point that ought to be stressed. Many of the pain-relieving drugs can produce a rise, though maybe not excessively high, of both serum amylase and serum lipase; and until you have drawn blood for these, you should try to control the pain with Demerol, if possible.

DR. LAKE: I think one point that should be stressed is that the rise in amylase is a transient rise, that if you get the serum within 24 to 48 hours you may find elevation and in 72 hours even though the person is sicker, it may have returned to normal.

MODERATOR WILKINSON: *Are there any other laboratory procedures you would like to suggest in acute pancreatitis?*

DR. LAKE: I think in acute pancreatitis you have a clinical picture which may, and often does, resemble that of a perforated viscus, that of intestinal obstruction and sometimes that of a coronary attack. There are tests which may help you eliminate the probability of these other conditions, such as x-ray, to see if there is free air beneath the diaphragm, the electrocardiogram which however in pancreatitis may show changes suggestive of a coronary occlusion. A rise in blood sugar sometimes accompanies an attack of pancreatitis.

MODERATOR WILKINSON: *Also sugar in the urine may occur, may it not?*

DR. LAKE: Yes, sugar in the urine. But I think the clinical picture is more important than the tests.

MODERATOR WILKINSON: I would agree with that, from the point of view of the internist.

Dr. Porter, how do you feel about the clinical picture as compared with the laboratory test in making the diagnosis?

DR. PORTER: I think the test, the amylase test, bears the same relation to the diagnosis of acute pancreatitis as the white count does to acute appendicitis. I think there are times when one might be inclined to diagnose acute pancreatitis though the test was not impressively high and there might be times when it might be prudent to ignore the elevation. Perhaps it should be mentioned that at our hospital we do not regard as unequivocally abnormal any amylase level that isn't at least twice our established normal,—that a slight figure above the normal printed in the circular does not necessarily mean that it is significant. We use M and K units.

MODERATOR WILKINSON: *It is my understanding that at New York Hospital it was four times the standard normal, is that correct?*

DR. LAKE: I don't know that we have any rule about it.

MODERATOR WILKINSON: I think certainly that elevations of one or two, two or three times the normal of the hospital, should be viewed with considerable reserve; and that when you get elevation due to an attack of acute pancreatitis it is usually sufficiently high so that one is in little doubt. *Dr. Hinton, have you anything to add here?*

DR. HINTON: I agree that the clinical picture of the hemorrhagic type of pancreatitis is by far the most accurate means of making the diagnosis. I think one other thing should not be forgotten, and that is an upper abdominal paracentesis is of real value because you may get hemorrhagic fluid in acute fulminating forms with a high amylase content. Regarding the 100 patients that I cited, none of them received either morphine or codeine. The only drugs that those postoperative patients with elevated amylase levels had received were atropine and Demerol.

MODERATOR WILKINSON: I think we will stay on the subject of acute pancreatitis for a few more minutes. *Dr. Lake, I wonder if you would begin the discussion on the treatment of acute pancreatitis.*

DR. LAKE: My feeling is that surgery should be avoided if possible. If you cannot exclude the possibility of a ruptured viscus you are of course forced to surgery. If an abscess develops you must operate, but if you are fairly certain of your diagnosis I think the patient should be put to bed, given nothing by mouth, perhaps use constant suction to stop the acids from stimulating secretin formation, replace fluids and electrolytes and give supportive treatment and wait. In a majority of cases the attack will subside on that regimen. Occasionally a jaundice will deepen, your patient will appear sicker and the question of whether or not he has a common duct stone will arise. We have seen such cases.

MODERATOR WILKINSON: *Do you give insulin for elevated blood sugar in such an attack?*

DR. LAKE: No, but you may have to give calcium if the calcium level drops.

MODERATOR WILKINSON: *Would you explain to the group some of the reasons why we think that the calcium level drops in these attacks?*

DR. LAKE: Some believe that if you have much fat necrosis the fat is split into fatty acid and glycerine and the fatty acid tends to combine with calcium to form soaps and if the area is extensive enough you may have enough calcium withdrawn from the rest of the body to cause a fall in the blood calcium level. That explanation is not universally accepted and there may be other factors.

MODERATOR WILKINSON: *Some people believe that as much as two or three grams of calcium might be deposited during an attack. Are these the deposits of calcium that we see later when x-rays of the pancreas are taken and show flakes of calcium throughout?*

DR. LAKE: Yes, in the area of fat necrosis you may get calcification later.

MODERATOR WILKINSON: *Do you believe that subsequent attacks are more likely when there have been attacks of pancreatitis?*

DR. LAKE: Yes. Whatever the cause of pancreatitis may be, I believe that deposits of calcium in and around the ducts may contribute to obstruction later and may in themselves be a source of trouble.

MODERATOR WILKINSON: *Dr. Porter, would you like to comment on this?*

DR. PORTER: On the treatment of acute pancreatitis I would add only a couple of things. One is that, used properly, chlorpromazine can be useful in intractable vomiting in these cases. They should receive

proper treatment for shock, including fluid therapy, when indicated. Personally, I think that, although this is not primarily a bacterial disease, it is prudent to use the antibiotics prophylactically to prevent the commonest complication which we see in acute pancreatitis, namely abscess.

MODERATOR WILKINSON: *Which would be the antibiotics of choice?*

DR. PORTER: Penicillin and streptomycin or one of the broad-spectrum antibiotics. It does not make much difference which of these is used in this situation.

MODERATOR WILKINSON: Certainly sometimes, and not infrequently, you do get invasion of *B. coli* so that it would be important to use one of the antibiotics to which *B. coli* would be sensitive.

DR. PORTER: I think that is fair. Penicillin and streptomycin in combination (perhaps by removing the organisms that go along with the *B. coli*) seem to control most of them fairly well. Another thing we do is to give vagolytic drugs parenterally to people who are nauseated and are vomiting, such things as parenteral Banthine or atropine. After the nausea and vomiting have subsided and we are able to give fluids again, we often give them Gelusil or other antacid along with the fluids in order to keep the acid in the duodenum to a minimum.

MODERATOR WILKINSON: There are some who use the double tube,—drip in a solution of sodium bicarbonate and keep it sucked out, in accordance with Dr. Lake's suggestion of the indwelling tube with constant suction.

DR. LAKE: Mr. Chairman, may I question some of this? I know that is the usual procedure. On theoretical grounds it is difficult for me to believe that a hemorrhagic pancreas is still producing enzymes, whatever the stimulus is. Can we get some comments on that?

MODERATOR WILKINSON: Yes.

DR. PORTER: May I make a comment since I have been worried about the enzymes? I would like to say that 99.9 per cent of the acute pancreatitis that I have seen has not been the acute hemorrhagic variety but a rather nasty kind that lays a fellow low but is not the catastrophic type mentioned by Dr. Hinton. The really bad one is quite rare,—certainly it is in our hospital,—so that I am a little confused as to which disease we are treating. I was talking about the garden variety, non-hemorrhagic acute pancreatitis.

MODERATOR WILKINSON: We are treating both kinds: edema with

some degree of hemorrhage, and then the so-called hemorrhagic type where you just have more of the same thing. To my way of thinking, it is a mistake to sharply differentiate the two because I think that they are both varying degrees of acute pancreatitis. The diagnosis may be missed if it is a mild attack and the patient may die from the same process if it is a severe attack. *Dr. Lake, do you believe there are actually two kinds of acute pancreatitis, one of them being the hemorrhagic type?*

DR. LAKE: I don't know. So far as we know at present they are just different degrees of the same disease.

MODERATOR WILKINSON: *Dr. Hinton?*

DR. HINTON: Speaking as a surgeon, they are definitely different. With regard to all forms of the acute type, the etiology of pancreatitis is certainly far from being understood. As Dr. Porter has stated, and speaking from my own experience, there are not many cases of the fulminating type of hemorrhagic pancreatitis. When you do see one you can usually make the diagnosis without the help of laboratory procedures. As I see it, it is a problem entirely different from that of the edematous pancreatitis.

MODERATOR WILKINSON: One point already mentioned which should be emphasized is that many attacks of acute alcoholism, with so-called alcoholic gastritis, have more the symptoms of acute pancreatitis than they do of acute gastritis. While in the Army I did pathology for a time and, on several occasions, did autopsies on soldiers who had been killed while driving cars at high speed and after consumption of considerable amounts of alcohol. I was impressed by the fact that, while there was hemorrhage and edema of the mucosa of the stomach, this was equalled if not exceeded by the edema and hemorrhage in the mucosa of the duodenum. In some of those cases that I examined postmortem, the pancreatic and bile duct sphincters were so edematous that it was hard to see how much could have gotten through. *Would you like to comment on that, Dr. Lake?*

DR. LAKE: I don't think it is entirely clear what the relationship of alcohol is to pancreatitis. There are some factors which Dr. Wilkinson has mentioned which are certainly operative. We know that alcohol stimulates formation of acid in the stomach. We know that it is an irritant and it may cause duodenitis, and in that way interfere with the flow of pancreatic juice. However, it may be that alcohol is actually a

poison to the pancreas and the liver tissue, or it may be that in chronic alcoholism there is a deficiency factor which may affect the pancreas as it does the liver. There is some evidence for that,—such as the ability to produce pancreatitis in animals by depriving them of the utilization of methionine. In several published series of autopsies on chronic alcoholics, the incidence of chronic pancreatitis is high. It is as high as 47 per cent in one series and 33 per cent in another. That may be a different disease than that of acute pancreatitis.

MODERATOR WILKINSON: I will try to sum up what we have said so far regarding treatment. First, nothing by mouth, except the stomach tube and gentle suction with or without soda bicarb going in; atropine or Banthine; no insulin, though the blood sugar may be high, unless a considerable degree of acidosis develops. The surgical approach should be conservative until the acute attack subsides. Does that suit most of the panel?

In chronic pancreatitis, for the purpose of this discussion, we can rule out the school of thought that considers so-called non-tropical sprue as a form of chronic pancreatitis. *Would any member of the panel object to ruling out non-tropical sprue? No objection? Then, Dr. Lake, would you tell us what you consider the etiological factors of chronic pancreatitis?*

DR. LAKE: I don't think they are known. As I said before, about half of them are associated with gallbladder disease, usually stones. However, chronic pancreatitis seems to be more common in males and gallbladder disease is more common in females. Chronic alcoholism seems to be a definite factor in chronic pancreatitis. Mechanical injury sometimes initiates repeated attacks of pancreatitis. Many cases of chronic pancreatitis have repeated acute or subacute attacks. However, there is a group without any history which may be found at autopsy. There is also a group of people who have vague symptoms, without ever being very sick, and finally, you find that they have calcification and they have diabetes so that it is not the result, in their case, of repeated necrotic episodes, but rather of some chronic, fibrotic process.

There are various theories. One is that obstruction at the sphincter of Oddi with reflux of bile into the pancreas is responsible for pancreatitis. I don't think bile has anything to do with it.

MODERATOR WILKINSON: *That is an interesting point of departure. Would you tell us why you think bile has nothing to do with it?*

DR. LAKE: We frequently see reflux of dye in cholangiograms in the pancreatic duct without pancreatitis. If you mix bile with trypsin it is not activated by bile. If you inject bile into the pancreatic duct, unless you use enough pressure to rupture some of the tissue, you don't get pancreatitis. If you use enough pressure you can cause pancreatitis with saline. There are some cases of pancreatitis where there is no common channel, anatomically.

MODERATOR WILKINSON: *Even if there is a common channel, you would have to have a common ampulla before you think of a reflux, would you not?*

DR. LAKE: Yes.

MODERATOR WILKINSON: *I believe that anatomically, the common sphincter without a common ampulla is probably more frequent than the channel with a common ampulla. Is that correct, a common sphincter without a common ampulla?*

DR. LAKE: I believe partial obstruction can cause pancreatitis. Whether in addition to partial obstruction, you need something that produces damage within the pancreas itself, which is capable of allowing pancreatic juice to leak out of the usual system, I don't know, but we have, for example, seen cases of carcinoma of the ampulla with repeated attacks of pancreatitis, where partial obstruction seemed to be the only factor.

MODERATOR WILKINSON: *Dr. Porter, do you want to comment on this?*

DR. PORTER: Yes. There has been an experiment recently and I have been shuffling my papers around here to see if I could find the names of the individuals who did it. I think they were Whitlock and Corckle who took goats, cut off the tail of the pancreas and plugged it into the gastrointestinal tract and tied off the common duct which is part of the common pathway with which I believe all goats are endowed,—at least a lot of goats,—anyway the goats these fellows used. In this way they effectively routed 100 per cent of the bile through the pancreas in order to get it out into the gastrointestinal tract. So in 100 per cent of these goats, bile traversed the pancreatic duct and out the back end to get into the gastrointestinal tract and the goats did not get pancreatitis. I think as far as the bile theory alone is concerned it is an interesting experiment. They would not have had such a happy set of goats had there been an element of obstruction. As is the case in any duct in

the body,—whether it be the Eustachian tube associated with otitis media or a blocked ureter associated with pyelitis, or any other tube associated with an "itis" behind it, they might have gotten pancreatitis had they had an element of obstruction, which I think is the important thing.

We have patients who have developed recurring pancreatitis behind benign tumors in the pancreas. May I mention one because it is a very interesting case? We had a lady about 40 years of age, who was having pancreatitis periodically. In fact it seemed to occur with her menstrual periods. We worked her up completely and could not find a single thing out of the way. Her biliary tract was normal on x-ray examination, as was the gastrointestinal tract. Her bouts of recurring pancreatitis were as unequivocal as they could be, associated with high elevations of serum amylase and with the usual clinical picture. We explored her upper abdomen with the intent of doing a choledochotomy and a transduodenal sphincterotomy. When we got into the abdomen we found the midportion of the pancreas was occupied by,—I was going to say by a tennis ball-sized, anyway it was a *darn* near tennis ball-sized cyst adenoma. There was pancreatitis to the left of it and completely normal pancreas to the right of it. We took out the tumor together with the indurated lefthand side and she has been well ever since. The interesting thing is that the pathologists are arguing about whether the cyst in question contained endometrium which would make it correlate with her menstrual period. Here is an example of a case in which the element of bile reflux did not enter into the individual's chronic relapses of pancreatitis, but where the element of obstruction was present however. Whether it was intermittent or not we are not too certain.

MODERATOR WILKINSON: *Dr. Hinton, would you care to comment on the effect of bile and/or obstruction in causing pancreatitis?*

DR. HINTON: I would be happy to do so. First I want to say that I am in complete accord with Dr. Lake, one of the few times in the history of the world that an internist and a surgeon have agreed on one factor in chronic pancreatitis. Before discussing humans, I would like to mention the experimental work of Mann and Giordano, published in 1923. They showed that, in the goat, the duct of Wirsung enters the common bile duct about 10 cm. above the duodenum. They ligated the goat's common duct so that all the bile could enter the duct of Wirsung. In none of these goats,—I believe there were five in all,—did they have

a death from pancreatitis. Of course, the situation is quite different when solutions are injected by syringe, using increased pressure.

In 1911, Nordman in Germany, did this in dogs. He ligated the ducts in dogs and these dogs, with the common duct completely ligated, did not get pancreatitis with normal intraduct pressures.

I would like to go back to the human. This problem has interested me for many years. With regard to the common channel theory, I feel there are a few fundamentals in human anatomy that are often completely forgotten by most of us surgeons, that involve the common channel theory. If you have read or if you care to read Opie's original report on Halsted's original case of acute hemorrhagic pancreatitis and the common channel theory, you will recall that Dr. Opie put pressure on the gallbladder at autopsy,—right, Dr. Lake?

DR. LAKE: Yes.

DR. HINTON: There is considerable question whether that bile was in the pancreas ante-mortem or post-mortem. That is one item. Another is that Dr. Opie did dissections on 100 humans. He found that it was possible for bile to flow back into the pancreatic duct in only 30 per cent of the 100 bodies examined. He also found that the pancreatic and the common ducts united so closely to the papilla that a stone as small as five millimeters would completely occlude the pancreatic duct. In 1911, Baldwin also found in another 100 humans, that in only 10 per cent was it possible for bile to flow back into the pancreatic duct because of the possibility of the opening of that duct at the papilla. Mann and Giordano, in 1922, in 200 humans, also presented essentially the same findings. In addition, and most important, they also found that, in their series of 200, the pancreatic duct entered the duodenum separately from the common duct in 31 per cent, thus eliminating in these the possibility of a reflux of bile into the duct of Wirsung. In Baldwin's 100 cases, separate openings of the pancreatic and common ducts occurred in 22 per cent. In Opie's original 17 cases of acute hemorrhagic pancreatitis he found a stone in the common duct in only two cases. To accept the common channel theory, which means that the common duct is the pipe line, the pancreatic duct is the feed line and your stone is your stopcock, takes more imagination than I have ever been able to muster.

MODERATOR WILKINSON: *Dr. Porter, I believe you mentioned, before the meeting began, the number of types of operations that have been*

performed for chronic pancreatitis. Would you care to discuss and recommend which procedure should be done in chronic relapses in chronic pancreatitis?

DR. PORTER: Up at P. & S. a few weeks ago we had what we call a Combined Clinic on pancreatitis. In preparing for the clinic I looked over the list of operations that Dr. Cattell of Boston has in his book, which incidentally is a good reference if you want a source-book on material relative to the pancreas. We were able to add several to Dr. Cattell's list and came up with something like 18 operations which are currently used, or advocated, or which have been used in the past in the treatment of chronic relapsing pancreatitis. I am sure each one has helped some individuals. No one of them is so sure-shot that you can be certain of the result or there would not be 18 of them in the list.

MODERATOR WILKINSON: We would not still be looking for new ones.

DR. PORTER: That is right. It is not as penicillin is to lobar pneumonia. I think it is perhaps more important to talk about one's approach to the problem than to blow the horn for any individual operation. We like to work the patient up and include in the workup a gastrointestinal series and gallbladder x-ray. If we find x-ray evidence of stones in the biliary tract we make up our minds to get rid of them. We know by so doing we help a lot of the individuals in question.

It is our custom, when we have decided to operate on a person with chronic relapsing pancreatitis, to go at it with the attitude of a person who is exploring the patient rather than entering the abdomen with the fixed conviction that one is going to do one particular procedure. We look at the pancreas for evidence of malignant or benign tumor (such as in the lady whose problems I told you about a minute ago) and we look at the gallbladder to see if it contains stones. If present, we take them out and explore the common bile duct and usually do a transduodenal sphincterotomy. If the gallbladder does not contain stones we are careful to leave it alone,—do not put clamps on it. That individual may develop a need for his gallbladder a few years hence. If his pancreas and lower bile duct are so scarred as to result in obstruction of the common bile duct, it may then be desirable to use the gallbladder for anastomotic purposes so we don't routinely remove the gallbladder. If the pancreas is normal as far as we can tell, we then enter the biliary tree and try to establish its normalcy through a choledochotomy. We

explore it up and down. If there are stones present we then take out the gallbladder. If no stones are present and we find the sphincter particularly tight we make a note of it, and in any event we do do a sphincterotomy. As a primary procedure in the typical case we do this and we find that we are (perhaps this is a guess because I have not added up our own hospital's data) helping, if not curing, a fairly large percentage of cases. If after these procedures they continue to have trouble, they become candidates for other operative procedures which we fit to their needs as we see them.

There are a few people, like the lady I mentioned to you, who require hemipancreatectomy for tumor. There are a few other peculiar situations which require types of treatment other than those I have mentioned. For instance, we have some individuals in whom there is a concurrent serious duodenal ulcer problem as well as pancreatitis. Such individuals might be treated by gastrectomy right off the bat. In general if you want to talk about the person who is the classical problem that everybody is worried about,—the fellow in whose instance you cannot find anything much,—that individual is treated by common duct exploration and transduodenal sphincterotomy as a first try, and then if he continues to have trouble, we go on and do some of the other operations which perhaps we can mention later.

One thing I would like to say is that I personally regard cases of pancreatolithiasis as somewhat apart from chronic relapsing pancreatitis as a clinical group. At least they are clinically different and certainly to the surgeon they present a somewhat different problem. So that what I have to say about chronic pancreatitis in general would not necessarily apply in our hospital to what we would do with a person with pancreatolithiasis.

MODERATOR WILKINSON: *Dr. Hinton, it is not fair to ask you to agree twice, so I will call on you at this point to discuss surgery of chronic pancreatitis.*

DR. HINTON: The choice of operative procedure in the surgical treatment of chronic pancreatitis is certainly debatable. From my observations, I do not believe that the duodenal ulcer pancreatitis is the type of pancreatitis that we have been discussing this afternoon. I have had a reasonably large experience in doing surgery for intractable chronic duodenal ulcer. In only one instance, in more than 500 cases, have I ever left the ulcer attached to the pancreas. By the same token,

in these intractable chronic ulcers the incidence of pancreatitis is certainly 75 per cent or better, at least it has been so in those that I have seen. The after results of the surgery of that type of pancreatitis do not cause the patient any more trouble and he is well after removing the ulcer, but the operation is not done for pancreatitis. You are operating for intractable ulcer and the pancreas forms the base of the ulcer. In only one instance have I seen a patient develop acute pancreatitis and that occurred some six months after a subtotal resection, the patient being perfectly well following the subtotal resection. We thought he had a ruptured gastrojejunal ulcer and it turned out that he had fat necrosis in his pancreas, the only one I have ever seen.

As to the other forms of pancreatitis, as Dr. Porter has said, there are many ways of approaching them, but the main objective in operating upon these patients is to relieve them of pain. Before this meeting began, Dr. Porter mentioned that many of these patients are drug addicts and to relieve them you must relieve the pain. I am not plugging for what I am about to say, having done only a few, but I believe Dr. Cattell refers to sympathectomy as an indirect method of attack on a complicated disease,—a viewpoint which I believe is correct. We have obtained some excellent results and I have become interested in sympathectomy as a means of relieving the patients of pain. One of our residents, Dr. Pfeffer, after spending three months working on the secretin test, selected ten normal patients without abdominal symptoms and another group of ten patients who averaged 4.8 years after vagotomy. The vagotomized patients had practically no pancreatic secretion, practically none. We also studied ten patients who had had a sympathectomy for essential hypertension and who had no complaints of intra-abdominal origin. This last group of patients had absolutely normal secretory studies, bicarbonate and amylase over an average period of 3.8 years. We have follow-ups on five patients with sympathectomies for chronic pancreatitis and the interesting thing to me is that the secretory activity of these patients with chronic pancreatitis—and some of these have been followed four years—has gradually diminished over the years, although the patients have been asymptomatic. One patient, who is the ambulance dispatcher at Bellevue Hospital, has had only a right sided sympathectomy for the calcareous pancreatitis but has now been well for four years in spite of the fact that he was an alcoholic and still is an alcoholic. I am interested in what Dr. Duvall

and Dr. Porter are doing at Presbyterian, and I am sure that Dr. Porter will describe that procedure a little later.

MODERATOR WILKINSON: *We will at this point present some of the questions that have come from the audience. The first one is: Is biopsy necessary at times to differentiate chronic pancreatitis from carcinoma of the pancreas?*

DR. PORTER: I knew somebody would ask that. I am sure that it is at times necessary to biopsy the pancreas in order to be certain. I will admit quite readily that we do not biopsy the pancreas often. We have found it to be an unprofitable, miserable, bloody, time-consuming procedure which is often wrong, for two reasons: The first one is that we do not take out representative sections. I have in mind one individual who was operated on first, I believe, by Dr. Parsons and then by Dr. John Lockwood and finally, by myself. In the course of the three operations we took 11 biopsy specimens, deep biopsies, all of which showed chronic pancreatitis. The individual eventually died and at autopsy we found him to have carcinoma of the pancreas. We just did not cut into the right spot where the carcinoma was associated with pancreatitis. That is the first thing. The second is that you may cut out a piece of tumor and the pathologist, however proficient he may be, may have a difficult time deciding in his own mind what he is looking at. I am not a pathologist but believe I am safe in saying that on occasion this is a particularly hard differential diagnosis for the pathologist to make. I have seen some good ones argue among themselves as to what was present. So it is our policy to make up our own minds based on clinical and operative findings as to which disease is present and whether or not it is operable. If we think it is a tumor and decide to go ahead with the resection, we do not biopsy. We make extended efforts to get biopsies if we deem them inoperable and are planning to leave the abdomen without removing the specimen. Would you be interested to know what our score is?

MODERATOR WILKINSON: Yes, I would be.

DR. PORTER: All right. In the last 54 resections for malignancies in this area with which I have had to do, I personally made the error of taking out one pancreas that had no tumor in it. I think Dr. Cattell has mentioned to me that his experience, although more extensive, is comparable. We miss them but we have stopped biopsying them in a routine fashion.

MODERATOR WILKINSON: *Dr. Hinton, here is a question directed to you: Is the presence of a rigid board-like abdomen a prerequisite for the diagnosis of acute pancreatitis? How often is the relatively soft abdomen present?*

DR. HINTON: The patients whom I have seen with acute hemorrhagic pancreatitis have a pain which no sedation will relieve. You may have to give them a quarter-grain of morphine every hour or two. They do have a rigid abdomen. You will secure a flat plate of the abdomen to rule out or at least to help rule out a perforated viscus. These patients appear much sicker than many patients with a perforated viscus, are frequently cyanotic, and they may have blue finger tips and often look as if they have a cardiac disease. If you note the excruciating pain and the general appearance of the patient, then you may make the reasonably accurate diagnosis of acute hemorrhagic pancreatitis. What to do for the patient is left to the internist.

MODERATOR WILKINSON: *Dr. Lake, would you discuss the secretin test.*

DR. LAKE: The secretin test is of great value in diagnosing some cases of chronic pancreatitis. Its limitations are that it is a difficult test for both the patient and the doctor who is getting the specimens and for the laboratory. You need a special laboratory setup. The reagents must be mixed freshly each time and the tests have to be run promptly. The specimens must be kept chilled while you collect them so that it pretty well kills the day to do a test. However, I will say again it is of great value in a large proportion of patients with chronic pancreatitis.

MODERATOR WILKINSON: *Another one for you, Dr. Lake: Is there any experimental basis to support the feeling among some that serum albumin should be used in the treatment of acute pancreatitis because of its antitrypsin effect?*

DR. LAKE: I don't know of any good experimental basis for it. It is of value in restoring blood volume.

MODERATOR WILKINSON: *Dr. Porter: In emotionally induced attacks, what is, first, the natural process and, second, the mechanism?*

DR. PORTER: That is what I get for mentioning the lady who fought with her husband! I can only say that one can assume that such an emotional upheaval could induce spasm—perhaps in the ampulla, perhaps in the pancreatic ducts themselves and perhaps in the vessels of the pancreas. One way or another this lady certainly, and with great

regularity, would come in with a typical acute pancreatitis.

MODERATOR WILKINSON: *You don't want to tell us the mechanism?*

DR. PORTER: That is the mechanism as I see it, but this is theory, not necessarily factual.

DR. HINTON: May I make a comment on that, Mr. Chairman? There is some experimental evidence to suggest that there is uropepsinogen release from the stress mechanism by ACTH. Some animal experimentation that we have done indicates that the release of ACTH by the anterior pituitary may be a factor in this syndrome. So, this rage and stress and strain may come about through the activity of the anterior pituitary. I am just talking off the cuff. I am not explaining.

MODERATOR WILKINSON: *Following cholecystectomy for cholecystitis and cholelithiasis, what is the frequency of pancreatitis? Dr. Lake, would you care to comment on that?*

DR. LAKE: I think one of the surgeons can perhaps answer that better than I. Do you mean to ask what is the percentage of people who have not had it before who get it after cholecystectomy?

MODERATOR WILKINSON: Yes.

DR. LAKE: I think many people have attacks of pain which are attributed to the gallbladder and after the gallbladder is removed the pain may continue. Originally there may have been other causes, one of which could be pancreatitis. I don't think removing the gallbladder would induce pancreatitis.

MODERATOR WILKINSON: *Dr. Porter, how do you feel about that?*

DR. PORTER: I have no idea what the number might be, except that it is fairly well known that pancreatitis as a complication of obstruction of the bile duct due to gallstones is a pretty rare complication indeed. If you take the number of people who are admitted with obstructed bile ducts as their primary trouble and check the percentage of them who have pancreatitis at that time, you find it is rare. I don't know what the answer is. Pancreatitis as a late sequella to cholecystectomy would make me suspect an overlooked "ball valve" common duct stone —a situation in which intravenous cholangiography is most useful.

MODERATOR WILKINSON: *Do you have an answer?*

DR. HINTON: Dreilling and Hollander at Mount Sinai Hospital published a paper a few years ago on the post-cholecystectomy syndrome in 98 patients. They did secretin studies to try to determine the role, if any, of the pancreas in this symptom complex. In these 98 patients

I believe the average postoperative period was 5.8 years. In only two instances were there abnormal secretin determinations, one of which had a carcinoma of the pancreas and in the other the findings indicated a chronic pancreatitis.

MODERATOR WILKINSON: *I think it is now time to ask the panel members if they would like to ask other members of the panel a question.*

DR. PORTER: In treating these relapsing pancreatitis patients it is our custom to try first to set the biliary tree to rights. If that does not do it, we do other things and among those we do sympathectomies. We have had failures. The patients may be all right for a year and then after that go back to drug addiction. We cannot be certain which was the chicken and which was the egg,—whether they went back to addiction because of pain or vice versa. We give them the credit and assume the pain returned as they say. What is the percentage of failures after sympathectomy done for pancreatitis?

DR. HINTON: This afternoon I talked with one of our residents who has followed these patients. We have not seen any real failures in those with a true pancreatitis. Some of them have gone as long as five years. It does not mean that they will not fail. Some of them are as recent as a year and one patient is as recent as two months,—but the overall picture is rather encouraging. Please understand that I am not advocating sympathectomy as the treatment of choice in pancreatitis.

DR. LAKE: Mr. Chairman, may I make a comment on that?

MODERATOR WILKINSON: Yes.

DR. LAKE: Where the acute attacks with fever and fat necrosis have subsided and pain remains, I think the results are good in our experience because it will stop visceral pain. Where you still get recurrent attacks of an acute nature, with fever, fat necrosis, fluid in the peritoneal cavity, you will not get complete relief because the parietal pain will not be relieved. For that reason Dr. Bronson Ray is conservative about doing sympathectomies on patients with acute episodes.

MODERATOR WILKINSON: Our experience on the Fourth Medical Division at Bellevue Hospital has been similar. The patient who seems to have chronic pain without really acute flare-ups is helped tremendously by the sympathectomy.

DR. PORTER: May I ask another question?

MODERATOR WILKINSON: Yes.

DR. PORTER: Dr. Hinton, how do you attack pancreatolithiasis in a person who has pain? There is the occasional patient who has the disease and is asymptomatic. He is not the one that is the problem.

DR. HINTON: The ambulance dispatcher at Bellevue Hospital, previously mentioned, was treated for 20 years for duodenal ulcer and presumably had the duodenal ulcer when he was admitted to our surgical service. He had chronic intractable pain. He did not have acute attacks. I believe that patient is now five or six years postoperative. At operation he had a pancreas full of calculi so that one could see the whole outline of the pancreas. We see this patient frequently and we know he is well.

MODERATOR WILKINSON: *He had two or three previous operations, did he not?*

DR. HINTON: That I cannot tell you. I am getting older and my memory is not too good.

MODERATOR WILKINSON: I think he was the one we sent you from our wards.

DR. HINTON: He may have been but he is now well—I know that. We get him back regularly and he is kind enough to come in whenever we wish to show him. We plan to restudy him next week with x-rays.

MODERATOR WILKINSON: *Dr. Hinton, do you have any questions to ask?*

DR. HINTON: I think Dr. Porter should say a few words about the operation which he and others at Presbyterian Hospital are doing, on anastomosing the tail of the pancreas to the upper gastrointestinal tract.

DR. PORTER: Only if I may preface it by stating that it is not our original idea. The chaps up at the Veterans Hospital in the Bronx did it first. The same week that they began doing it for logical reasons, we stumbled into it for other reasons. We tried to do a total pancreatectomy on a person with pancreatolithiasis. However, we found the pancreas so firmly glued to the portal vein that we decided to settle for as much pancreas as we had already mobilized. This we removed but we were then faced with the imminence of a fistula. We thought we would treat the fistula before it developed, so we pulled a Roux limb up and put a back door (as the house staff says) to the pancreas and that individual has enjoyed relief from the symptoms of pancreatolithiasis which brought him to us in the first place. This has been a pleasant surprise.

We did the second case a week later. We intended to do a total pancreatectomy, something we have done in the past for pancreatoli-

thiasis, and which works. It is a big undertaking. It certainly helps these people if you pull the trick off all right, so we did the operation again. That individual did not get relief and later I believe, committed suicide or died, one or the other. Since then we have done several others deliberately because by then we had heard about the work being done up in the Bronx and it seemed like a good thing to try out. We have had some pleasing results to date. In essence, as we have approached it, it is an attempt to take out every bit we could without getting into major difficulty or a big operation. In the last one we did, we took out the pancreas just over to the duodenum, leaving enough pancreas to cover the bile duct, making it unnecessary to do any anastomosis of any type —leaving the little nickel's worth of pancreas there. We put the Roux limb up to that to prevent leakage or other difficulty and that individual has enjoyed complete relief although he was really miserable before operation. I think the procedure has merit and in time we will learn when to use it. I don't think that it is going to be any "penicillin" for these people because it really should not work in people with 'lithiasis. Their secondary ducts are blocked,—the little side branching alleyways, but it is a handy thing to have available and it can get a surgeon out of the abdomen, when he is left with the end of the pancreas looking at him, without having to ultimately return to repair a fistula.

MODERATOR WILKINSON: *Dr. Lake, I think you have a question?*

DR. LAKE: I would like to come back to the question of sphincterotomy. Dr. Porter stated that when they open the duodenum and don't find anything else, they do a sphincterotomy. I remember doing a gastrointestinal series on a patient who had had a sphincterotomy and I was amazed to see the barium fill up all the liver bile radicles. It seems to me cholangitis could easily result from such a procedure if it were done in a liberal fashion. The results I have seen after sphincterotomy have not been uniformly good. I would like to ask for some more comment from the surgeons on that. If a large percentage of these people have obstruction within the pancreas, certainly sphincterotomy theoretically will not help them.

DR. PORTER: As to the barium in the liver matter,—I have not seen it in a sphincterotomy patient, but I have seen it in other people and in our experience it does not necessarily mean that those individuals are going to be more subject to cholangitis than others. The factors that are necessary include not only access to the liver on the part of

the soup and potatoes but also an *obstructive element*. Let the ducts stenose and develop a little back pressure and you have cholangitis. We are necessarily alarmed because the barium goes back up the ducts.

I cannot tell you what percentage of our patients who have had sphincterotomies for pancreatitis, enjoy relief,—I am sure nowhere near as good as Dr. Hinton's results from sympathectomy. I would guess that we see an end to the disease in probably 50 to 75 per cent of our patients who have their biliary tree set to rights, the stone-containing gallbladder removed, the stone-containing common duct cleaned out and the sphincter taken care of at the same time. The remaining 25 per cent we go about treating with one of the other methods such as sympathectomy or some of the other less well known methods.

DR. LAKE: Do you feel that the sphincterotomy adds anything to what you otherwise do to the biliary tract?

DR. PORTER: I think it does. I believe we have seen it unequivocally help individuals. I am not aware of any complications due to sphincterotomy, except as technical errors may have been made. I feel that trans-choledochosphincterotomy is something that I would not use because one may cut more than he intends to or in a direction that he'd rather not. We make it a practice to do it under direct vision when we do it. The favorite route is via the duodenum.

MODERATOR WILKINSON: *Dr. Hinton, we have time for one more comment. Will you proceed?*

DR. HINTON: We ought to remember,—though most surgeons probably know it,—that three deaths following sphincterotomy occurred at a Los Angeles hospital. The three deaths following the operation were due to acute hemorrhagic pancreatitis. Even though the end results in those who survive may be completely satisfactory, the procedure is not entirely free of danger.

MODERATOR WILKINSON: Our time is up and I want to thank the members of the panel for their cooperation and their stimulating discussion, and the audience for its interest and attention.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION*

Presented at the Meeting, April 28, 1955, at The New York Academy of Medicine

Cytology of Esophageal Washings: Evaluation of 364 Cases

WILLIAM D. JOHNSON, LEOPOLD G. KOSS, GEORGE N. PAPANICOLAOU and JOHN F. SEYBOLT

Memorial Center for Cancer and Allied Diseases and New York Hospital-Cornell Medical College

Three hundred and sixty-four cases were reviewed in which esophageal washings had been studied cytologically either at the Strang Laboratory of Cytology, Memorial Center for Cancer and Allied Diseases, or at the Papanicolaou Cytology Laboratory, New York Hospital-Cornell Medical College. The purpose of this study was to investigate the characteristics of normal and abnormal esophageal cytology, and to evaluate the usefulness of cytology in the diagnosis of esophageal cancer.

Specimens from the normal esophagus showed in smears superficial squamous epithelial cells, smaller numbers of deeper squamous cells, and occasional blood cells, histiocytes, and cells from the respiratory tract.

Specimens from cases of chronic esophagitis were usually more cellular, with an increased proportion of the deeper squamous cells, and many leukocytes. Many of the epithelial cells showed morphologic abnormalities, and in three cases of chronic esophagitis false-positive diagnoses of cancer were made,—the only false positives in the series. Study of surgical and autopsy material from these cases suggested that in chronic esophagitis there is a loss of the more superficial cells from the squamous epithelium of the esophageal mucosa, with marked morphologic abnormality among the cells remaining. One case showed squamous metaplasia of esophageal glands. The misinterpreted cells in the smears might have come either from the surface or from the glands.

Specimens from cases of malignant tumor of the esophagus usually contained relatively few tumor cells. In this series there were 148 cases of primary malignant tumor of the esophagus, of which 142 were epidermoid carcinomas, five adenocarcinomas, and one a malignant melanoma. Some of the epidermoid carcinomas yielded well-differentiated cells showing keratinization of cytoplasm; in others the cells showed no specific differentiation. The adenocarcinomas yielded cells with hyperchromatic nuclei and extensively vacuolated cytoplasm. The cells from the malignant melanoma showed no melanin and resembled cells of poorly-differentiated epidermoid carcinoma.

Of the 148 cases of primary malignant tumor of the esophagus, 103 (69.7 per cent) were diagnosed by cytology as positive for malignant cells, 18 (12.1 per cent) as suspicious, and 27 (18.2 per cent) as negative.

The series included 81 cases of malignant tumors primary outside of the esophagus. Twenty-five of these, most of which were gastric tumors with esophageal extension,

* Manuscripts received July 1955.

were diagnosed as positive for malignant cells, while 12 were diagnosed as suspicious, and 44 as negative.

The series included 135 cases in which no malignant tumor was found. Of these, three (2.2 per cent or 0.8 per cent of the total series) were falsely diagnosed as positive for malignant cells, as noted above. Seven were diagnosed as suspicious and 125 as negative.

Comparison of results of cytology and of biopsy in the 148 cases of primary esophageal tumor showed that of these cases 117 had positive biopsies (79 per cent) and 18 cases had negative biopsies only, while in 13 cases no biopsy was taken. In 18 cases (12.1 per cent) cytology made the diagnosis of cancer when biopsy was either negative or not done.

The authors concluded from these findings that cytology forms a useful adjunct to biopsy in diagnosing cancer of the esophagus, since cytology made the diagnosis in some cases of this series where biopsy failed to do so. Cytology should be of particular value in cases where biopsy is not practicable. The importance of severe chronic ulcerative esophagitis as a cause of false positive diagnosis was stressed.

BIBLIOGRAPHY

Andersen, H. A., McDonald, J. R. and Olsen, A. M. Cytologic diagnosis of carcinoma of the esophagus and cardia of the stomach, *Proc. Mayo Clin. 24*:245-53, 1949; and Cytologic diagnosis of malignant lesions of the esophagus and cardia of the stomach, *Minn. Med. 32*: 1181-85, 1949.

Bablik, L. Die Cytologie des Oesophagus-Carcinoma, *Arch. f. Ohr., Nas. u. Kehlk.-Heilk. 161*: 295-301, 1952.

Brenner, S. A. Cytologic diagnosis of esophageal cancer; a case report, *J. Amer. med. Wom. Assoc. 7*:123-26, 1952.

Calvert, J., Marquès, P., Biraque, C., Planel, H. and Azais, C. Le cytodiagnostic du cancer de l'œsophage, *Bull. Assoc. franç. Cancer. 40*:39-44, 1953.

Imbriglia, J. E. and Lopusniak, M. S. Cytologic examination of sediment from the esophagus in a case of intra-epidermal carcinoma of the esophagus, *Gastroenterology 13*:457-63, 1949.

Imbriglia, J. E., Stein, G. N. and Lopusniak, M. S. Cytological study of the upper gastrointestinal sediment; its value, as correlated with roentgenologic and clinical findings, in the diagnosis of cancer, *J. Amer. med. Assoc. 147*:120-22, 1951.

Lorber, S. H., and Shay, H. Intubation technique for obtaining material from the esophagus for cytologic examination, *Gastroenterology 14*:395-97, 1950.

Messelt, O. T. Cytologic diagnosis of esophagus cancer, *Acta chir. scand. 103*:440-41, 1952.

Panico, F. G. Cytologic patterns in benign and malignant gastric and esophageal lesions, *Surg., Gynec. Obstet. 94*:733-42, 1952.

Pfaltz, C. R. and Probst, R. Die normale und pathologische Cytologie des Bronchialsekretes und der Oesophagusschleimhaut, *Arch. Ohr-Nas. u. Kehlk.-Heilk. 164*:255-96, 1953.

Pricolo, V., Baglioni, T. and Amisano, G. Citodiagnosi dei tumori dell' esofago, *Tumori 37*: 401-14, 1951.

DISCUSSION

EDITH E. SPROUL: We have had no experience with esophageal washings, and I am interested in the technique of obtaining the material. I think that is half the battle, so that since no one is obtaining specimens of this kind in our hospital we have not been able to study aspirations. I will corroborate the statement about the failure of biopsies in this part being cases in which there was inflammation. We have been puzzled as to just what was seen by the surgeon when he took the biopsy specimen and why he took this particular spot in which he insists there was obviously a cancer, and it is true in many instances that although cancer was there, all they have obtained in the biopsy specimen showed the inflammatory reaction in the neighborhood of the cancer.

An Evaluation of the Concomitant Use of Smear and Cell Block Techniques in the Diagnosis of Cancer

HOWARD L. RICHARDSON, THOMAS R. SIMON and LEOPOLD G. KOSS

Memorial Center for Cancer and Allied Diseases

The cytologic examination of fluids by means of sample smears, no matter how carefully prepared, leaves behind a large residue which might contain valuable diagnostic material. In order to evaluate this residual material it was decided to treat it as a cell block, embed it in paraffin, and examine sample sections, in addition to the routine smears.

The fluids are submitted to our laboratory with previously added alcohol in various concentrations as recommended by Papanicolaou.[1] Particles contained in sputum are smeared directly. Fluids other than sputum are centrifuged for one-half hour at the rate of 2,500 revolutions per minute. The supernatant is discarded and the sediment smeared. Four smears are prepared from each specimen and stained according to the method of Papanicolaou.[1] The material remaining after preparation of the smears is placed in porous filter paper which in turn is enclosed in a small wire mesh box. The specimens destined for cell blocks are fixed in a solution of 13 gm. of picric acid in 1,000 cc. of 70 per cent alcohol for four hours or more. The fixation is followed by dehydration and embedding. Nine to 12 sections, placed on three or four slides, are cut and stained with hematoxylin-orange G-eosin, according to the technique described by Richardson et al.[2]

TABLE I—RESULTS OF SIMULTANEOUS USE OF SMEARS AND CELL BLOCKS

Total patients investigated: 2,076 Total specimens investigated: 2,613

Designation of Specimen	*No. of Patients with Cytologically Proven Malignant Tumors*	*Total No. of Positive Specimens*	*Cell Block and Smear Positive*	*Smear Alone Positive*	*Cell Block Alone Positive*
Sputum	144	232 100%	107 46%	96 41%	29 12%
Bronchial Washings	47	51 100%	33 69%	6 12%	10 19%
Naso-Tracheal Washings	8	10 100%	7 70%	3 30%	0
Miscellaneous (Mostly esophageal washings)	35	36 100%	28 78%	6 17%	2 5%
Pleural	124	184 100%	124 67%	41 22%	19 10%
Abdominal	44	55 100%	40 73%	10 18%	5 9%
Gastric	5	5 100%	2 40%	1 20%	2 40%
Urine	5	5 100%	3 60%	1 20%	1 20%
Totals	412	578 100%	346 60%	164 28%	68 12%

Two thousand, six hundred and thirteen fluid specimens from various sources were examined by both smear and cell block techniques. Table I summarizes the results. Only the unequivocal results were charted as positive; suspicious or atypical smears or cell blocks were charted as negative.

In the entire group of 578 positive specimens smears failed in 12 per cent, and in these cases the correct diagnosis was made by means of cell blocks. The impression gained is that the highest degree of accuracy will be achieved by utilizing smears as the principal diagnostic weapon and supplementing them with cell blocks of material remaining after the preparation of smears.

REFERENCES

1. Papanicolaou, G. V. *Atlas of exfoliative cytology.* Cambridge, Mass., Harvard University Press, 1954. (Commonwealth Fund Publication.)
2. Richardson, H. L., Queen, F. B. and Bishop, F. H. Cytohistologic diagnosis of material aspirated from stomach, *Amer. J. clin. Path. 19*:328-40, 1949.

DISCUSSION

N. CHANDLER FOOT: I am not officially scheduled to open this discussion, but I would like to do so. The matter of cell blocks has always been one in which I am very much interested, and I agree wholeheartedly with what Dr. Simon has said. One reason why smears are sometimes difficult to read is that one rolls up material into thick ridges in which interpretation is often difficult; another one is that the cells in a smear are spread out widely and you have to do a good deal of searching to find them, so that for the lazy man the cell block is superior, as he does not have to work so hard to find his cells. Another point to be remembered is that after you prepare your smears quite a residuum of sediment is left unused—why not block this and make sections? You are just discarding useful material if you throw what remains down the sink. In some instances a tumor may be recognized in a cell block and missed in the smears; I am surprised that the percentages of cells missed in sections of blocks and recognized in smears alone ran as high as they did: I expected that the reverse would be true. I was also surprised to find that this also happened in the case of bronchial washings. There is, however, no doubt in my mind that the cell block has been neglected and should be more often adopted and energetically used.

There is another point about cell blocks: if someone wants to have duplicates of your smears you cannot furnish them because you cannot spare them from your collection, but if you have a cell block in paraffin it is perfectly easy to cut sections and send them off. You can get great numbers from a cell block, so that your material is then more or less permanent and can be subjected to special stains if you want to demonstrate certain things. That is difficult to do in the case of smears unless you have a great many of them.

As to tumors missed in smears, there is a case in point: in going over a great many sediments of transudates and exudates there was one case in which the tumor was completely missed in smears, but in the cell block one small, unmistakable fragment proved to be present. That is one of the "pick-ups" that may be credited to the old cell block method, so that I urge you all to keep it in mind and to apply it. I'm not saying that you should give up the use of smears; I do not mean that at all; on the contrary, I think that we should use both methods and check the results against each other.

DAVID P. SEECOF: I would like to add a few words to what Dr. Foot said in relation to several items dealing with the issues involved. Historically, I would like to call attention to the fact that over 31 years ago, on January 10, 1924, I presented a paper[1] before this Society in which the findings were reported on all sorts of fluids examined by a routine cell block method. At that time the percentage of correct results averaged 70 per cent. I have had practically no experience at all with the smear method, but would like to make a few remarks of a general nature based on over 30 years of cell block study. First, we cannot expect to get 100 per cent correct results from cytologic methods because it cannot be done 100 per cent on good H & E sections, when

diagnosing malignancy. As was pointed out in the paper, "Unlike bacterial examinations, in the absence of a specific stain for tumor cells, these cannot be entrusted to persons who are not familiar with at least the general microscopic characteristics of malignancy." Secondly, the experienced pathologist, accustomed to well fixed and H & E-stained preparations, loses his skill in recognizing malignancy when handed slides treated differently. At this point I would like to recall an episode encountered with the late Dr. Francis Carter Wood. When asked how does he recognize a cancer or a cancer cell, he said: "The only way I can explain it is to say that it is like recognizing my uncle, in the largest group of people. I might describe him to you so that you could pick him out in a small group, but no matter how long I might describe my uncle to anybody he would not be able to spot him in the subway." Philosophically, it seems to me that the 30 per cent deficiency in the cytologic methods of diagnosing cancer represents the degree of our ignorance on the whole subject of cancer and shows up in all the figures of cytologic successes as only 70 per cent correct diagnoses.

H. P. SMITH: I am curious to know how many use the two methods of cell block and smear, as has been advocated. Can we have a show of hands? (About 15 members of the audience raised their hands). That is a pretty large number, and is very interesting.

REFERENCE

1. Seecof, D. and Boetsch, N. The value of examining body fluids for tumor cells, *Proc. N. Y. Path. Soc.* 24:2-9, 1924.

Some Pitfalls of the Cytologic Diagnosis of Cancer

LEOPOLD G. KOSS

Memorial Center for Cancer and Allied Diseases

The purpose of this paper is to present a series of observations made on cytologic material originating in the respiratory tract with emphasis on potential sources of error in the diagnosis of lung cancer.

All of the cellular elements seen in smears can, at one time or another, be mistaken for cancer cells.

Squamous epithelial cells may show marked abnormalities in the presence of inflammatory disease of the buccal mucosa. Radiation changes may be also observed and may be quite misleading, although the squamous epithelium may be actually outside the direct field of irradiation. These latter changes are in all respects similar to those seen in vaginal smears following radiation.

Respiratory epithelial cells may present a variety of misleading atypias: densely packed clusters of small cells with hyperchromatic nuclei may be noted. Such cells represent multiplication of reserve cells of the bronchial mucosa. They can be differentiated from cancer cells more readily by appearance of the clusters in smears than by their cellular characteristics. Occasionally benign bronchial cells show prominent nucleoli. In bronchiectases quite misleading clusters of vacuolated cells forming papillary structures sometimes can be noted. Absence of necrosis and of anisocytosis may prove of value in distinguishing these cells from those of adenocarcinoma. Squamous metaplasia of bronchial lining, not an infrequent finding in chronic bronchitis and bronchiectases, is another potential source of erroneous diagnosis of cancer. Tracing the origin of such clusters by finding cilia and terminal bars is helpful in making the diagnosis.

Radiation effects on respiratory epithelium constitute a very important group of atypias. These effects can be recent and manifest themselves in multinucleation. In cases with past history of radiation striking changes may occur: the presence of highly keratinized atypical small cells, singly and in clusters, may prove to be very troublesome in making the differential diagnosis. In case of doubt repeat examinations are advised.

Of other atypical cells occurring in smears one should mention atypical macrophages which may possess large atypical nuclei of peculiar uniform structure. The origin of these cells is unknown. One should also mention the fact that vegetable cells when occurring singly may occasionally simulate cancer cells. Cytoplasmic granules will usually render the differential diagnosis easy.

These remarks represent an effort to sum up a variety of cytologic atypias which may simulate cancer. It is obvious, however, that no amount of descriptive writing will replace experience in dealing with the difficult but rewarding field of cytologic diagnosis of lung cancer.

DISCUSSION

N. CHANDLER FOOT: Dr. Koss has brought out the main pitfalls very cogently; he has brought out those things which trouble us most in borderline cases. It would, however, be a pity if you all got the impression that all smears of sputum and bronchial washings that you examine will present these difficulties; fortunately they don't. A great many of them show cancer cells and show them unmistakably, so that their recognition is not difficult in the majority of instances. It is the minority that show these changes. Personally, I have just finished going over a lot of these smears in which sputum or bronchial washings furnished the material and published a paper

in the Journal of Clinical Pathology[1] which has just come out. In the course of this investigation the thing that bothered me the most was the question: "What is normal bronchial epithelium?" Recourse to histologies is not too satisfactory; they do not describe this epithelium very well, and it is only when you consult huge systems of text-books like von Möllendorf's series in German that you find the respiratory epithelium adequately described. The important point about it is that the layer of deep cells, or "reserve cells", as Halpert calls them, lie below the ciliated cells on the surface; there are two layers of them: a deeper one that resembles lymphocytes and a more superficial one comprising increasingly larger cells. Clusters of cells from either layer are dislodged by the bronchoscope and are very readily mistaken for cancer cells. It is only by studying normal histology and establishing standards that you can hope to be at all sure of what you are doing in diagnosing bronchial washings.

The obvious error is that a lot of these cells are taken for small-celled anaplastic carcinoma, which is a great mistake. In that tumor the cells are of different sizes and shapes and they are very numerous in the smear. Furthermore, they should show the phenomenon that Dr. Koss spoke of: they should be loosely separated from one another rather than being closely packed and apposed. I think that the theory as to reserve cells coming up from the basal layer and changing their shape as they do, and the possibility of bronchogenic carcinomas developing from any one of these developmental stages, is very interesting. In studying a section of a cat's bronchus, given me by a fellow instructor as "normal bronchus", I found to my great surprise areas of complete metaplasia, so that anyone looking at them would diagnose "carcinoma *in situ*." But this was an example of metaplasia, or extreme atypia, attributable to inflammation, which Dr. Koss has described very thoroughly.

One of the most puzzling things that one finds is the cell that results from bronchiectasis; Dr. Koss went into this *in extenso*. It might interest you to learn a little of the history of the discovery of that cell. The first examples we saw at New York Hospital, Dr. Papanicolaou discovered in the sputum of a child about four years of age. He mistook it for a cancer cell, showed it to me, and so did I. I consulted Dr. Stewart as to whether children four years old could have bronchogenic carcinoma; he said that he had seen one or two cases, which did not help us very much! Later on we found that the child had well-developed congenital bronchiectasis, which was the answer to our problem. From then on, Dr. Papanicolaou continued to recognize cells from bronchiectatic cavities. I have found them a fertile source of error in interpreting sputum and bronchial washings.

The matter of multinucleated bronchial respiratory epithelial cells mentioned by Dr. Koss is very interesting. In examining the series on pulmonary carcinoma I purposely excluded all knowledge of clinical data on the cases; all I knew was the number of the case, smears of which I was investigating. The phenomenon of multinucleation was puzzling, and I am interested to know that it is a possible result of irradiation. It is quite true that I noted it most often in specimens that came from Memorial Hospital, where irradiation is largely indulged in.

The orangeophilia of cells in epidermoid carcinoma, while not in and of itself indicative of malignant tumor, is a very good clue. We find small orangeophilic cells with small pyknotic nuclei in smears of sputum and the moment we note them look farther for more typical and decisive cells, which are usually to be discovered elsewhere in the smear. While unjustified in making a diagnosis of epidermoid carcinoma on a basis of the presence of these small cells alone, we are nevertheless alerted by them to examine the specimen carefully, and often find "the real thing."

Dr. Koss' giant macrophages are very interesting; we have seen very few of the extreme examples that he showed us. Those that occur in connection with lipoid pneumonia are very distinctive and once noted are readily identified in future examinations. They take on extremely large size, become very bizarre and, at first, may be very startling until you know with what you are dealing.

EDITH E. SPROUL: The discussion has brought up the question of the advantages and disadvantages of smears and cell blocks, but I do not believe we have had any discussion of different stains. Are all these Papanicolaou stains? At the Francis Delafield Hospital we started out doing smears and cell blocks and routinely did a Papanicolaou, H & E, and mucicarmine stain on all of them. I have gradually dropped the Papanicolaou and maintained the others, partly I suppose because I agree with the story that was told and am sufficiently old-fashioned to have more background with the H & E stain with which I can compare these smears. On the other hand, if the Papanicolaou stain has advantages over the others, I am glad to know of them.

JACOB M. RAVID: This brings us back to the problem of smears versus cell blocks in the general field of cytologic diagnosis of fluids. In my own experience, whenever possible, I resort to both methods, as on several occasions where the smears were negative, the cell blocks proved to be positive for neoplastic cells.

I should also like to touch upon the problem of ciliated cells in connection with cytologic examination of bronchial secretion. It would appear that, since cilia are a most differentiated feature of the bronchial cells, one should not expect to find them in connection with cancer cells. In spite of this, and as we saw in some of the photomicrographs this evening, we find that occasionally some malignant-appearing cells still have a ciliated or brush-like border. I should therefore like to ask Dr. Koss what is his experience in this respect, and how often did he find such a ciliated border with cancer cells.

LEOPOLD G. KOSS: To answer the first question about the stains, we have also tried both stains for a while, but what we dropped was the H & E. We feel we are getting distinctly better detail by using a modified Papanicolaou stain for cell blocks; it is an H & E-orange G stain that is somewhat lighter. For smears we just use the Papanicolaou stain; we like it quite well. It gives excellent differentiation of the cytoplasm, which H & E does not.

EDITH E. SPROUL: Have you tried the mucicarmine stain? It gives you the advantage of picking up some mucin occasionally.

LEOPOLD G. KOSS: We are set to do that; we shall soon.

The second question concerning the ciliated cells is a very interesting one. We have had long discussions on the subject with my chief, Dr. Stewart, as well as among ourselves, and the only case of a metastatic malignant tumor I distinctly remember where cilia were present was a metastatic muco-epidermoid carcinoma. I have never seen convincing malignant cells with cilia in sputum. I do not think I would dare make a diagnosis of carcinoma on ciliated cells in the sputum. I do not know whether they ever occur.

REFERENCE

1. Foot, N. C. Cytologic diagnosis in pulmonary cancer, *Amer. J. clin. Path. 25*:223-40, 1955.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION*

Presented at the Meeting of May 26, 1955, at The New York Academy of Medicine

The Development and Prevention of Fatty Livers of Portal Type

WELLINGTON B. STEWART

The Department of Pathology, College of Physicians and Surgeons, Columbia University

A fatty liver in which fat accumulates in the portal region of the lobule has been consistently produced in rats. This was done by feeding a diet in which the sole source of protein was derived from plants.[1] The diet was similar to that consumed in regions where the human disease kwashiorkor is prevalent, and, moreover, the hepatic lesion resembles that seen in kwashiorkor. It is not yet known, however, whether the disease thus produced in rats is truly an experimental analogue of the human disease.

After one week on the diet, small droplets of fat are visible in the hepatic cells that lie near the portal connective tissue. The amount of fat then increases over a 12 week period. The droplets become larger, and new droplets appear toward the central region. Finally the entire lobule may be involved. Whether this lesion will progress to cirrhosis is not yet known.

Attempts to prevent the development of the fatty liver were made by supplementing the diet with various compounds. The addition of the usual "lipotropic" substances—choline, methionine, and vitamin B_{12}—was ineffective.[2] Several amino acids were then added to the diet.[3] It was found that lysine and tryptophane prevented the accumulation of fat in many, but not all, of the rats. Simultaneous addition of both amino acids seemed to be somewhat more effective than either alone, but, still, a few rats had increased hepatic lipids. Threonine was ineffective, either alone or together with methionine.

The curative effect of these compounds is currently under investigation. Preliminary data suggest that lysine and tryptophane may cause the regression of the hepatic lipid accumulation as well as prevent its accumulation.

REFERENCES

1. Shils, M. E., Friedland, I. and Stewart, W. B. Rapid development of portal fatty liver in rats consuming various plant materials, *Proc. Soc. exp. Biol. Med. 87*:473-76, 1954.
2. Shils, M. E., De Giovanni, R. and Stewart, W. B. Fatty liver of portal type; effects of choline, methionine, and vitamin B_{12}, *J. Nutr. 56*:95-106, 1955.
3. Shils, M. E. and Stewart, W. B. Preventive influence of certain amino acids on experimental fatty liver of portal type, *Proc. Soc. exp. Biol. Med. 87*:629-31, 1954.

DISCUSSION

JOSEPH POST: I am much interested in Dr. Stewart's paper, because our group has been concerned with related studies for some time. The observations presented here establish a biologic significance for amino acids, beyond the earlier concepts of their support of growth. I am especially interested in the fatty liver which does not respond to choline.

Some of the studies of Patek et al.[1] have shown this in a different way. The experimental fatty cirrhosis of rats fed a low protein diet responds better to a high protein diet than to choline or methionine feeding.

Our group[2] has shown that in human alcoholics the lipotropic action of a diet of about 50 grams of protein cannot be aug-

* Manuscripts received August 1955.

mented by the addition of large amounts of dietary choline.

These studies suggested that dietary protein contributed more than its choline. It is probable that in the impure dietary deficiency of human alcoholics, amino acid deficit may play a significant role.

Several questions have occurred to me:

1. What was the general clinical state of these deficient rats?

2. Was any attempt made to feed the different groups isocalorically? This is a most important control.

3. Will the cirrhosis which eventuates be healed by amino acid repletion?

4. Do the fatty livers of amino acid deficiency show alterations in phospholipid turnover similar to those in choline deficient fatty livers?

Finally, I should like to thank Dr. Smith for his gracious invitation and for the privilege of participating in this most stimulating evening.

WELLINGTON B. STEWART: These animals are in a poor nutritional state. The diets are relatively low in protein and growth is poor. Moreover, there are frequently changes in the color and consistency of the hair, and loss of hair.

The animals have not been "pair fed". We have used, instead, littermate controls and reasonably large numbers of animals.

We have had no opportunity to study any biochemical changes in the livers. That is something we hope to do.

MAX WACHSTEIN: My question is related to Dr. Post's first question. I wonder how much of the fatty liver is a starvation effect in general and not due to a specific amino acid deficiency. In this connection I would like to know what the tryptophane content was of the diet used by you. Since you relate your experiments to kwashiorkor, it is obvious that one would be interested to know whether the pancreas showed significant microscopic changes.

WELLINGTON B. STEWART: I am certain the fatty liver is not related solely to starvation. We have done experiments to rule out this factor.

We have not done amino acid analysis on our diets, but the proteins used are known to be deficient in these amino acids. That is one of the reasons we tested those we did. We have not seen, as yet, any pancreatic damage that I can recognize. That is one of the reasons we are being cautious about claiming that this is experimentally the same disease as kwashiorkor.

MAX WACHSTEIN: We have worked on the problem of producing pancreatic damage not only by ethionine, but also by trying to produce it by dietary means only.[3] Rats on a diet which does not contain any protein at all but all other necessary nutritional elements show regularly within 30 days severe pancreatic atrophy and fibrosis. A supplementation with 4 per cent casein will almost completely prevent any pancreatic damage.

ARTHUR SCHIFRIN: Has this liver change been produced in dogs and puppies?

WELLINGTON B. STEWART: We have not tried them as yet.

HENRY SIEGEL: What is the incidence of lung disease in these rats?

WELLINGTON B. STEWART: This is a strain which seems to be very resistant to lung disease, even in the old rats. Our rats are only a few months old when we dispose of them, and there is no evidence of lung disease.

H. P. SMITH: That is the strain of rats which has been bred selectively in order to secure resistance to lung infections?

WELLINGTON B. STEWART: No, it is not that strain.

H. P. SMITH: Have any efforts been made to treat the human disease with amino acids?

WELLINGTON B. STEWART: As far as I know, no such attempts have been made. The feeding of powdered skim milk is said to cure the disease, however. Often the children are so critically ill that experiments do not seem to be justified.

REFERENCES

1. Plough, I. C., Patek, A. J., Jr. and Bevans, M. The relative effects of protein, choline and methionine in the treatment of experimental dietary cirrhosis in the rat, *J. exp. Med. 96:* 221-31, 1952.
2. Post, J., Benton, J. G., Breakstone, R. and Hoffman, J. The effects of diet and choline on fatty infiltration of the human liver, *Gastroenterology 20*:403-10, 1952.
3. Wachstein, M. and Meisel, E. Relation of dietary protein levels to pancreatic damage in the rat, *Proc. Soc. exp. Biol. Med. 85*:314-17, 1954.

NEW YORK PATHOLOGICAL SOCIETY

ABSTRACTS OF PAPERS AND DISCUSSION*

Presented at the Meeting of May 26, 1955, at The New York Academy of Medicine

The Development and Prevention of Fatty Livers of Portal Type

WELLINGTON B. STEWART

The Department of Pathology, College of Physicians and Surgeons, Columbia University

A fatty liver in which fat accumulates in the portal region of the lobule has been consistently produced in rats. This was done by feeding a diet in which the sole source of protein was derived from plants.[1] The diet was similar to that consumed in regions where the human disease kwashiorkor is prevalent, and, moreover, the hepatic lesion resembles that seen in kwashiorkor. It is not yet known, however, whether the disease thus produced in rats is truly an experimental analogue of the human disease.

After one week on the diet, small droplets of fat are visible in the hepatic cells that lie near the portal connective tissue. The amount of fat then increases over a 12 week period. The droplets become larger, and new droplets appear toward the central region. Finally the entire lobule may be involved. Whether this lesion will progress to cirrhosis is not yet known.

Attempts to prevent the development of the fatty liver were made by supplementing the diet with various compounds. The addition of the usual "lipotropic" substances—choline, methionine, and vitamin B_{12}—was ineffective.[2] Several amino acids were then added to the diet.[3] It was found that lysine and tryptophane prevented the accumulation of fat in many, but not all, of the rats. Simultaneous addition of both amino acids seemed to be somewhat more effective than either alone, but, still, a few rats had increased hepatic lipids. Threonine was ineffective, either alone or together with methionine.

The curative effect of these compounds is currently under investigation. Preliminary data suggest that lysine and tryptophane may cause the regression of the hepatic lipid accumulation as well as prevent its accumulation.

REFERENCES

1. Shils, M. E., Friedland, I. and Stewart, W. B. Rapid development of portal fatty liver in rats consuming various plant materials, *Proc. Soc. exp. Biol. Med. 87*:473-76, 1954.
2. Shils, M. E., De Giovanni, R. and Stewart, W. B. Fatty liver of portal type; effects of choline, methionine, and vitamin B_{12}, *J. Nutr. 56*:95-106, 1955.
3. Shils, M. E. and Stewart, W. B. Preventive influence of certain amino acids on experimental fatty liver of portal type, *Proc. Soc. exp. Biol. Med. 87*:629-31, 1954.

DISCUSSION

JOSEPH POST: I am much interested in Dr. Stewart's paper, because our group has been concerned with related studies for some time. The observations presented here establish a biologic significance for amino acids, beyond the earlier concepts of their support of growth. I am especially interested in the fatty liver which does not respond to choline.

Some of the studies of Patek et al.[1] have shown this in a different way. The experimental fatty cirrhosis of rats fed a low protein diet responds better to a high protein diet than to choline or methionine feeding.

Our group[2] has shown that in human alcoholics the lipotropic action of a diet of about 50 grams of protein cannot be aug-

* Manuscripts received August 1955.

mented by the addition of large amounts of dietary choline.

These studies suggested that dietary protein contributed more than its choline. It is probable that in the impure dietary deficiency of human alcoholics, amino acid deficit may play a significant role.

Several questions have occurred to me:

1. What was the general clinical state of these deficient rats?

2. Was any attempt made to feed the different groups isocalorically? This is a most important control.

3. Will the cirrhosis which eventuates be healed by amino acid repletion?

4. Do the fatty livers of amino acid deficiency show alterations in phospholipid turnover similar to those in choline deficient fatty livers?

Finally, I should like to thank Dr. Smith for his gracious invitation and for the privilege of participating in this most stimulating evening.

WELLINGTON B. STEWART: These animals are in a poor nutritional state. The diets are relatively low in protein and growth is poor. Moreover, there are frequently changes in the color and consistency of the hair, and loss of hair.

The animals have not been "pair fed". We have used, instead, littermate controls and reasonably large numbers of animals.

We have had no opportunity to study any biochemical changes in the livers. That is something we hope to do.

MAX WACHSTEIN: My question is related to Dr. Post's first question. I wonder how much of the fatty liver is a starvation effect in general and not due to a specific amino acid deficiency. In this connection I would like to know what the tryptophane content was of the diet used by you. Since you relate your experiments to kwashiorkor, it is obvious that one would be interested to know whether the pancreas showed significant microscopic changes.

WELLINGTON B. STEWART: I am certain the fatty liver is not related solely to starvation. We have done experiments to rule out this factor.

We have not done amino acid analysis on our diets, but the proteins used are known to be deficient in these amino acids. That is one of the reasons we tested those we did. We have not seen, as yet, any pancreatic damage that I can recognize. That is one of the reasons we are being cautious about claiming that this is experimentally the same disease as kwashiorkor.

MAX WACHSTEIN: We have worked on the problem of producing pancreatic damage not only by ethionine, but also by trying to produce it by dietary means only.[3] Rats on a diet which does not contain any protein at all but all other necessary nutritional elements show regularly within 30 days severe pancreatic atrophy and fibrosis. A supplementation with 4 per cent casein will almost completely prevent any pancreatic damage.

ARTHUR SCHIFRIN: Has this liver change been produced in dogs and puppies?

WELLINGTON B. STEWART: We have not tried them as yet.

HENRY SIEGEL: What is the incidence of lung disease in these rats?

WELLINGTON B. STEWART: This is a strain which seems to be very resistant to lung disease, even in the old rats. Our rats are only a few months old when we dispose of them, and there is no evidence of lung disease.

H. P. SMITH: That is the strain of rats which has been bred selectively in order to secure resistance to lung infections?

WELLINGTON B. STEWART: No, it is not that strain.

H. P. SMITH: Have any efforts been made to treat the human disease with amino acids?

WELLINGTON B. STEWART: As far as I know, no such attempts have been made. The feeding of powdered skim milk is said to cure the disease, however. Often the children are so critically ill that experiments do not seem to be justified.

REFERENCES

1. Plough, I. C., Patek, A. J., Jr. and Bevans, M. The relative effects of protein, choline and methionine in the treatment of experimental dietary cirrhosis in the rat, *J. exp. Med. 96:* 221-31, 1952.
2. Post, J., Benton, J. G., Breakstone, R. and Hoffman, J. The effects of diet and choline on fatty infiltration of the human liver, *Gastroenterology 20*:403-10, 1952.
3. Wachstein, M. and Meisel, E. Relation of dietary protein levels to pancreatic damage in the rat, *Proc. Soc. exp. Biol. Med. 85*:314-17, 1954.

Cholestatic Hepatitis (Primary Pericholangitis; Cholangiolitic Hepatitis)

I. N. DUBIN*

Armed Forces Institute of Pathology, Washington, D.C.

The problem of the existence of "cholangiolitic hepatitis" as an entity stems from two types of clinical cases: (a) a type that early in its course resembles obstructive jaundice, as judged by liver function tests, and (b) another that manifests itself as prolonged jaundice (which again raises the question of obstruction). After studying such cases and comparing them with viral hepatitis, drug hepatitis and many other forms of liver disease, I suggest the following tentative conclusions: 1) There is a form of primary hepatic disease that resembles obstructive jaundice (sometimes clinically, sometimes histologically, sometimes both) that we may designate "primary pericholangitis", "cholangiolitic hepatitis", or, preferably, "cholestatic hepatitis". 2) It seems to be a form of viral hepatitis, as Eppinger[1] suggested. 3) It is probably a disease of both the parenchymal cells and the intrahepatic bile ducts and not of the latter structures alone; hence my preference for the term "cholestatic hepatitis", signifying a form of hepatitis characterized by intrahepatic bile stasis. 4) A similar clinicopathologic picture may be caused by certain drugs and perhaps by hormones.

Our current concepts of the histologic picture of viral hepatitis are too narrow:[2] we admit to this category only cases that show a severe diffuse parenchymal crumbling and inflammation, and omit others that either have leukocytes in the portal tracts or prominent intrahepatic bile stasis with relatively mild parenchymal inflammation. Yet, a study of a large group of cases indicates that viral hepatitis presents a broader spectrum of histologic change than we have been willing to recognize. At one end of the spectrum is the classic picture of viral hepatitis, — diffuse parenchymal inflammation and piecemeal necrosis, degenerated and necrotic liver cells, acidophilic cells, bizarre regenerating cells, pigmented macrophages, and many mononuclear cells in parenchyma and portal tracts. At the other end the histologic picture is that of "cholestatic hepatitis" (cholangiolitic hepatitis), — the intrahepatic bile ducts intimately surrounded by a few inflammatory cells (neutrophilic leukocytes prominent), relatively mild focal necrosis and inflammation of parenchyma, and a moderate degree of intrahepatic bile stasis. Between the two ends of the spectrum there are many cases that present a mixture of all of these histologic features, so that one can begin with the classic picture of viral hepatitis and by imperceptible shades move to that of cholestatic hepatitis without loss of continuity. For the moment, this is the only working hypothesis that will satisfactorily explain the large mass of clinical, chemical and pathologic data that have been amassed in the field of viral hepatitis.

I have seen the clinicopathologic picture of cholestatic hepatitis caused by drugs also, perhaps on the basis of an allergic reaction: such drugs are arsphenamine, carbarsone, chlorpromazine, propyl-thiouracil, tapazole, isoniazid, phenylbutazone, para-aminosalicylic acid and phenurone. Undoubtedly there are others.

There is a third group of "cholestatic hepatitis" that is probably caused by hormones. This group includes (a) the lesion produced by methyl testosterone, (b) recurrent jaundice associated with pregnancy, and (c) hepatitis and primary biliary cirrhosis occurring in middle-aged women.

All three types of primary cholestatic hepatitis may run an acute self-limited course; and indeed most cases do. A small proportion of cases, however, is more prolonged and persists for months or even years. Finally I have seen a rare case progress to fatal liver failure with a histologic pic-

* Now at Woman's Medical College, Philadelphia, Pa.

ture of cirrhosis.

In the differential diagnosis of primary cholestatic hepatitis one must consider secondary pericholangitis, the cholestasis of hepatic failure and, most important of all, obstructive jaundice.

"Pericholangitis" (acute inflammation surrounding the intrahepatic bile ducts) may be hematogenous, or may be secondary to a disorder of the extrahepatic bile ducts. The former type may be seen in association with systemic infections, cachexia or cancer; in this type there are neutrophilic leukocytes in portal areas, and small foci of parenchymal necrosis; but fortunately intrahepatic bile stasis is absent, so that the problem of obstructive jaundice or primary cholestatic hepatitis does not arise. The other form of secondary pericholangitis follows certain non-obstructive inflammations of the gallbladder and extrahepatic biliary tract, pancreatitis, and perhaps even duodenal lesions. Perhaps it comes about by retrograde lymphatic spread. In this form also intrahepatic bile stasis seems to be absent. This type of lesion can progress to a form of biliary cirrhosis without intrahepatic bile stasis.

Intrahepatic cholestasis of liver cell failure should not be confused with primary cholestatic hepatitis, because the former can occur whenever the liver cells fail, as in acute alcoholic necrosis, toxic hepatitis and episodes of hepatic decompensation in portal cirrhosis.

The great difficulty comes in distinguishing primary cholestatic hepatitis and obstructive jaundice. A comparison was made of liver biopsy specimens of 83 cases of obstructive jaundice with those of 30 cases of "cholangiolitic hepatitis" in which no obstruction was found at exploratory laparotomy. Bile lakes, bile granulomas and cholangitis (exudate within the lumen of intrahepatic bile ducts) occurred *only* in the cases of obstructive jaundice. Unfortunately these helpful diagnostic criteria occurred only late and infrequently in the course of obstructive jaundice. Bile lakes occurred in 14 per cent, bile granulomas in 21 per cent and cholangitis in 9 per cent of biopsy specimens; but none of these features appeared before the fourth week of clinical jaundice. Pericholangitis, on the other hand, was an early complication of obstructive jaundice and was present in all cases, thereby enhancing the resemblance between obstructive jaundice and cholestatic hepatitis. This difficulty was aggravated by the fact that in obstructive jaundice parenchymal lesions mimicking those of cholestatic hepatitis soon supervened; in the centrolobular zones (the site of bile stasis) there were focal necrosis and inflammation of parenchyma in about half the cases, and the liver cells were distorted, pleomorphic, acidophilic, foamy, and bile-stained. It is noteworthy, however, that in obstructive jaundice the focal necrosis tended to be limited to the areas of bile stasis while in primary cholestatic hepatitis the necrosis occurred haphazardly in the lobule and bore no relationship to the localization of the bile plugs. Also, in cholestatic hepatitis the bile plugs tended to be fewer and generally smaller than in obstructive jaundice. Of the 30 cases of cholestatic hepatitis there were seven cases in which the intrahepatic bile stasis was so pronounced that these cases may readily have been misconstrued as obstructive jaundice (extrahepatic biliary obstruction). Nevertheless, using the differential histologic points mentioned above, a pathologist with considerable experience in interpreting liver biopsy specimens could probably distinguish primary cholestatic hepatitis from obstructive jaundice in about 70 per cent of cases.

DISCUSSION

HENRY G. KUNKEL: It is certainly a privilege to listen to Dr. Dubin's description of some of the studies that he and his associates have been carrying on at the Army Institute of Pathology. One might say that they are in the process of rewriting hepatic pathology on the basis of their very extensive combined use of biopsy as well as autopsy material. Studies in the past on cholangitis and pericholangitis have been particularly confusing, not only because of the nomenclature, but also because of the violent disagreement between different pathologists who have been involved in these cases. For example, the

relatively simple pathologic picture of early cholangiolitic cirrhosis that MacMahon and Thannhauser[8] presented as a specific lesion has been vigorously attacked by other workers. The old question of whether one can differentiate a primary lesion in or about the small bile ducts within the liver cell that gives a picture of obstructive jaundice, from a secondary reaction to an extrahepatic obstruction has remained a controversial point for many years. The paper has clarified this point and has indicated that there is certainly some specificity involved. Particularly interesting, I think, is this known sensitivity to certain drugs and chemicals that Dr. Dubin has mentioned as a causative factor in producing an obstructive picture clinically in certain patients. We have encountered cases as a result of sulfonamides, arsenic, methyl testosterone, phenylbutazone and a number of others, particularly the very common one at the present time, chlorpromazine. One of the interesting things in this reaction is that occasionally these people develop a high eosinophil count at the very time they become jaundiced. This is further evidence for a specific sensitization to these materials rather than a direct toxic effect.

I think anybody who has observed viral hepatitis will subscribe to the idea that in certain cases the classical manifestations of hepato-cellular damage are scarcely evident, while the signs, the symptoms and the laboratory findings of obstructive jaundice predominate. Some of these cases probably show the pericholangiolitic lesions described tonight.

While certain drugs and infectious hepatitis appear to be etiologic agents in producing an obstructive jaundice picture, a number of other cases, particularly those developing a severe primary biliary cirrhosis, remain of unknown etiology. A possible etiologic clue to this cholangiolitic hepatitis or cirrhosis is the female incidence in the general population, suggesting the possibility of hormonal effect. Knowing Dr. Dubin's primary source of materials at the Army Institute of Pathology, such a sex incidence would hardly be expected in his cases, although I did see eight females in his group of 30 cases. I would be interested to hear comments on this reported female predominance in the general population.

I. N. DUBIN: I am happy to see that Dr. Kunkel, as clinician, can subscribe to my views that have been reached from experience as pathologist. It is interesting that clinician and pathologist, starting with different disciplines, should reach similar conclusions. As regards the question of sex incidence of cholestatic hepatitis, I agree that eight women of a total of 30 cases suggests a preponderance in the female sex, because most of our pathologic material at the Armed Forces Institute of Pathology comes from men. Forty per cent of our material in the Hepatic Pathology Section comes from the Armed Forces and their dependents, 50 per cent from veterans, and 10 per cent from civilian sources. But I would rather go through our entire group of 150 cases before making a final statement about sex incidence.

MARVIN KUSCHNER: I think one might preface any discussion by a semi-serious plea to Dr. Dubin to rush this paper into print and thus protect us from the surgeons who, influenced by less unprejudiced reports, insist on throwing on the pathologist the responsibility of deciding whether or not a patient should be operated on. The extent of the responsibility is perhaps indicated by the fact that three out of 30 patients died, which looks like a rather high mortality rate for ordinary hepatitis. The particular question I have is as follows: In the group of 30 cases, seven were thought to be "misconstruable" as cholangitis, but this was on the basis of wedge biopsy specimens. I wonder if Dr. Dubin would estimate how well he would do on needle biopsy material.

I. N. DUBIN: Starting with the last question first: Some cases were studied both by needle and surgical biopsy specimens, and some by needle biopsy only at the time the abdomen was opened; I looked at these biopsies and asked myself, "If these liver specimens came to me only as needle biopsy specimens without the belly having been opened, how well could I do in distinguishing

obstructive jaundice from cholestatic hepatitis?"

Well, it seems to me I might well have missed the diagnosis in seven of the 30 cases. Whether I would have, I do not know. But I know I have made mistakes in the past, mistaking obstructive jaundice for cholestatic hepatitis, and vice versa. I have the impression that when my studies are completed I may be able to make the correct diagnosis in about 70 or 80 per cent of cases. Accordingly, I do not think the responsibility should be taken off the pathologist's shoulders; I believe it is still our responsibility to do as well as we can, and I think we can do reasonably well.

As regards the mortality rate in our group of 30 cases, I do not think we can draw conclusions from our series as to the danger of operating upon such patients. The patients were old; all were seriously ill. From the appearance of the biopsy specimens I would guess that they would have died anyway from severe hepatitis even if they did not suffer the additional trauma of an exploratory laparotomy.

PETER GRUENWALD: The surgeons say that in some of these cases in which the abdomen is opened with the diagnosis of obstruction and then no obstruction is found, the patients do particularly badly postoperatively, and their mortality is very high. Can you confirm that?

I. N. DUBIN: I can only say from my experience, which is limited to a study of the clinical summaries—I have not seen the patients myself—that I have the impression that some do remarkably well after they have their bellies opened. The danger of unnecessary operation should not be minimized; yet I cannot help thinking that this danger is sometimes unconsciously exaggerated by the surgeon in order to transfer further responsibility to the pathologist. Certainly there is a risk in operating upon some of these older persons and the patient should be spared the burden of unnecessary operation; still, all we as pathologists can do in this very difficult field is make our best effort in interpreting these needle biopsy specimens; if we cannot be certain, or if our efforts do not suffice, then the surgeon must do an exploratory laparotomy to determine whether or not obstruction is present.

THOMAS G. MORRIONE: I do not know whether Dr. Dubin will accept the credit for this as an observation on his part: We have been interested in the phenomenon of reversible versus irreversible cirrhosis. Experimentally, I am quite certain that marked cirrhosis can occur in animals, verified by quantitative chemical collagen determination, producing even a four-fold increase in connective tissue. This cirrhosis may disappear, and this regression of cirrhosis has been observed as an experimental phenomenon in rats. There has been a great deal of reluctance to accept the possibility that this phenomenon may occur at all in humans. About five years ago I asked Dr. Smetana whether he had observed any evidence that in certain instances of cirrhosis, connective tissue could be resorbed from human livers. At that time he stated that he had not observed this phenomenon. I notice that Dr. Dubin avoided calling cases which I would consider cirrhosis as "true cirrhosis" because he felt that these patients recovered. In effect, if his demonstration of reversible cirrhosis is true, and if he would be willing to commit himself to that extent, to my knowledge this would represent an extremely important and long-awaited observation. This would represent the human counterpart of reversible experimental cirrhosis in animals. I may have been wrong in some of my concepts in the past in that I have concluded on the basis of experimental data that we gathered that some of these experimental cirrhoses that regressed did so because the hepatic cells themselves had retained their ability to regenerate, and that in prolonged cirrhosis, the cirrhosis becomes irreversible because the hepatic cells lose their ability to regenerate. There is recent evidence from Gross and his group in Boston that alterations in the solubility of collagen may play an extremely important role in this phenomenon. We are learning that though collagen has traditionally been regarded as an insoluble protein, it is not

only soluble in dilute acids, but even soluble, as Gross has recently shown, in dilute saline. One can recover proline from extracts of collagen, and we have found that the connective tissue of infants is very soluble, whereas the connective tissue of adults is not. We believe that livers which show reticulum as the predominant component of the stroma are those which are most apt to be "reversible". When one sees a picture such as Dr. Dubin showed of the trichrome preparation, with abundant trichrome-positive material, one might assume that to be the classical Laennec's cirrhosis, and possibly irreversible. I wonder whether Dr. Dubin would care to comment on the phenomenon of reversibility of cirrhosis, and the possibility of this occurring in some forms or instances of human cirrhosis.

I. N. DUBIN: I think it is my duty to commit myself. As a result of my experience with serial biopsy in viral hepatitis, I believe that too much has been called "cirrhosis" which really never was cirrhosis. I myself know of no instance in man in which cirrhosis has disappeared. Lucke[4] showed that in viral hepatitis, as the liver cell dies, the reticulum surrounding each liver cell collapses; this results in a mass of condensed reticulum that has been mistaken for "collagen scars" or "fibrosis" or "cirrhosis". We know from electron microscopic studies that the reticulum fiber and the collagen fiber are structurally similar, except that the collagen fiber is made up of many smaller fibers, indistinguishable from reticulum fibers. Consequently it is not surprising to find that when many collapsed reticulum fibers are bunched together that such a bundle should give a reaction with a trichrome stain suggesting that the bundle is a mass of collagen. But if we do a reticulum stain in conjunction with the trichrome stain we can readily see that we are dealing only with collapsed reticulum, and the result of the trichrome stain is a false positive one. As long as these collapsed reticulum fibers are intact, the liver lobule can be restored to its original structure. As the liver cells regenerate, the reticulum fibers act as a scaffolding and guide the newly formed liver cells into the original anatomic relationship. The regenerating cells push the collapsed reticulum fibers apart, and, behold, the "scars" disappear! Perhaps the reticulum fibers have to be injured, chemically altered, or fused before they make a mass of collagen; but I strongly suspect that when true collagen is made (or laid down) in the liver, it does not disappear.

LOUIS ODESSKY: I would like to ask Dr. Dubin whether he makes any distinction between cholangitis and cholangiolitis.

I. N. DUBIN: Yes, I would prefer to use the term "cholangitis" for an inflammation of the bile duct resulting in an outpouring of exudate in the *lumen* of the bile duct. "Cholangiolitis" I would prefer not to use at all, because it has so many confusing connotations stemming from earlier writings. Perhaps we can do without it, and use Eppinger's[5] term "pericholangitis", indicating there is an inflammation surrounding the small intrahepatic bile ducts.

LOUIS ODESSKY: What are the limits you draw in microns between the smaller and larger bile ducts?

I. N. DUBIN: I have not measured them. When I say "the small intrahepatic bile ducts" I mean the smallest biliary structures we see in every portal canal, that are still lined by recognizable biliary epithelium.

MAX WACHSTEIN: If you have to decide on operation on a biopsy specimen, do you consider the laboratory findings in your evaluation of the tissue?

I. N. DUBIN: Yes, I like to use all the information available. As physicians we are all after the total picture presented by the disease process and not just that facet that is reflected by our individual discipline. I like the intellectual challenge of analyzing a liver biopsy specimen without clinical data, but when I get down to the serious business of proffering a diagnosis that may sway my clinical colleagues, I like to have all the information about the

patient that I can get. Of course, if the histologic picture is pathognomonic, I don't worry too much about the laboratory data. For example, if the biopsy specimen shows the classic picture of viral hepatitis of the diffuse parenchymal type, I am not sidetracked by an alkaline phosphatase of 60. By the same token, if I see a good bile lake, I know I'm dealing with obstructive jaundice regardless of what the laboratory tests may show. But unfortunately there are too many of the other type of case, in which the liver biopsy specimen will not stand alone; and in such an instance all the pathologist can do is put all the information together, give due weight to the various components, and make the most reasonable diagnosis.

REFERENCES

1. Eppinger, H. *Die Leberkrankheiten; allgemeine und spezielle Pathologie und Therapie der Leber.* Vienna, J. Springer, 1937.
2. Smetana, H. F., Keller, T. C. and Dubin, I. N. Histologic criteria for the differential diagnosis of liver diseases in needle biopsies, *Rev. Gastroent. 20*:227-38, 1953.
3. MacMahon, H. E. and Thannhauser, S. J. Xanthomatous biliary cirrhosis (clinical syndrome), *Ann. intern. Med. 30*:121-79, 1949.
4. Lucke, B. The structure of the liver after recovery from epidemic hepatitis, *Amer. J. Path. 20*:595-619, 1944.

VESALIAN ATLAS AND ESSAYS

A FEW READERS will remember the notable re-impression of the illustrations from Vesalius' *De fabrica* issued jointly by the libraries of the Academy and the University of Munich in 1934 under the title *Icones anatomicae*. Rediscovered in 1932 through an inquiry by Dr. Samuel W. Lambert, the original woodblocks of 1543, cut in the lifetime and under the eye of Vesalius, were painstakingly re-impressed by the Bremer Presse of Munich in order that these accurate and skillfully executed drawings, never yet surpassed, might be shown to the best advantage by the great improvements made in modern printing. The loss of the original woodblocks during the bombing of Munich in World War II is irreparable. It is fortunate, indeed, that new pulls of them had been made before disaster overtook them. A few copies of the *Icones* are still available at $95.00 from the Library of The New York Academy of Medicine.

The production of this atlas naturally occasioned much consideration of Vesalius' work. The discovery of the blocks had in fact come about through Dr. Lambert's search for the original cuts of Vesalius' historiated initial letters on which he was then working. Three of the essays resulting from these studies have since been printed in *Three Vesalian Essays*, 1952: S. W. Lambert, "The Initial Letters of the Anatomical Treatise . . . of Vesalius"; Willy Wiegand, "Marginal Notes by the Printer of the *Icones*"; and W. M. Ivins, Jr., "What about the *Fabrica* of Vesalius", an inquiry into the identity of the individual responsible for the advance of anatomical knowledge demonstrated in Vesalius' illustrations. The *Essays* may be had from the Macmillan Company for $6.00.

THE TWENTY-NINTH

ANNUAL GRADUATE FORTNIGHT

THE NEW YORK ACADEMY OF MEDICINE

OCTOBER 15-26, 1956

SELECTED SUBJECTS OF CURRENT SIGNIFICANCE

The Committee on Medical Education of the Academy, in an effort to make the 1956 Graduate Fortnight of greater value to the practitioner, has departed from the program format of former years. Instead of a comprehensive development of a single subject, reports on five general topics of special current importance will be presented and the total number of Fortnight sessions will be reduced. The program will consist of a series of three lectures per session on five alternate evenings, and panel meetings and clinical pathological conferences on five alternate afternoons. In these presentations, the basic work and practical applications of recent advances in these subject areas will be evaluated and summarized. As heretofore a Scientific Exhibit will be on display throughout the Fortnight.

Registration for non-Fellows of the Academy, $10.00.

(Continued on next page)

TWENTY-NINTH ANNUAL GRADUATE FORTNIGHT (Continued)

I. GENERAL TOPICS

Lecture Sessions—three half hour lectures per session, on five alternate evenings:

1. The Place of Hypophysectomy and Adrenalectomy in the Management of Neoplastic and Metabolic Diseases
2. New Drug Therapy in Psychiatry and Hypertension
3. An Evaluation of the Present Status of Cardiac Surgery
4. The Adrenal Cortical Steroids and their Analogues
5. Poliomyelitis

II. PANEL MEETINGS AND CLINICAL-PATHOLOGICAL CONFERENCES

To be held on five alternate afternoons:

1. The Management of Disseminated Neoplastic Diseases (Panel)
2. Malignant Hypertension (CPC)
3. Surgical Management of Cardiovascular Disease (Panel)
4. Thyroid-Pituitary-Adrenal Disease (CPC)
5. Therapy of Infections (Tbc, Rickettsial, Staphylococci) (Panel)

COMPLETE PROGRAM TO BE ANNOUNCED LATER

For registration or application for exhibit space, address:

The Secretary, Graduate Fortnight

THE NEW YORK ACADEMY OF MEDICINE

2 East 103 Street : New York 29, N. Y.

IN X-RAY VISUALIZATION

Reduced Hypermotility, Improved Delineation with Pro-Banthine®: Case History

Basic film: pronounced hypermotility of stomach and bulb; diagnosis not possible.

Five-minute film after 15 mg. of Pro-Banthine intramuscularly: large gastric ulcer on lesser curvature clearly visualized.

J. R., male, age 50, when first seen* complained of severe abdominal pain of six weeks' duration. Initial gastrointestinal roentgenologic examination revealed marked hypermotility of the stomach and duodenal bulb. Because of rapid emptying it was not possible to visualize a lesion either in the stomach or duodenal bulb. However, the patient's symptoms strongly suggested an ulcer, and he was reexamined after the injection of 15 mg. of Pro-Banthine (brand of propantheline bromide) intramuscularly. A marked diminution in motility occurred and a huge gastric ulcer was easily visible on the lesser curvature at the junction of the upper and middle third of the stomach.

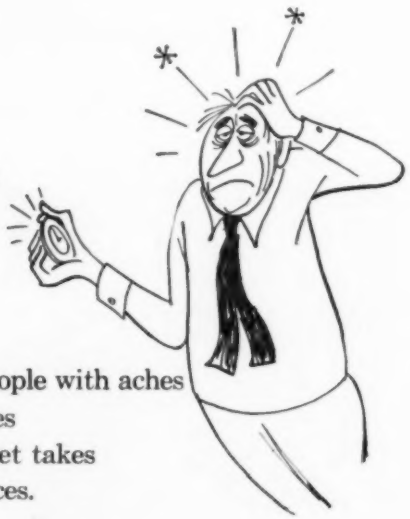
This patient is now receiving 30 mg. of Pro-Banthine four times daily and gained 8 pounds during the first ten days of therapy. He was completely relieved of pain within twenty-four hours. The ulcer is presently healed and he is asymptomatic, six weeks following initiation of Pro-Banthine therapy. This is an excellent example of delineation of a lesion which escaped detection with the ordinary technique of gastrointestinal roentgenography. If an ulcer is suspected and the initial roentgenologic examination is negative or inconclusive, the roentgenographic study should be repeated following the oral administration of 30 mg. or the intramuscular injection of 15 mg. of Pro-Banthine. G. D. Searle & Co., Research in the Service of Medicine.

*Roentgenograms and case history courtesy of I. Richard Schwartz, M.D., Kings County Gastrointestinal Clinic, Brooklyn, N. Y.

Trial packages of Pro-Banthine and the new booklet, "Case Histories of Anticholinergic Action," available on request...

SEARLE

P. O. Box 5110 C
Chicago 80, Illinois



GOT A STOP WATCH?

Verse by
RICHARD ARMOUR
Illustrations by
LEO HERSHFIELD

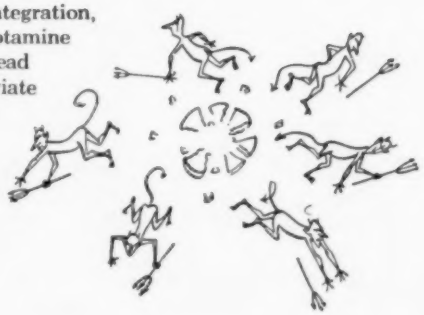
One thing that's important for people with aches
As awful as migraine produces
Is the time that the rescuing tablet takes
To dissolve in the gastric juices.

A tablet can drop to the stomach like lead,
End over end or revolving,
Then lie there like lead (oh, those pains in the head!)
And take its sweet time dissolving.

But Wigraine disintegrates quick as can be,
It doesn't just lie around lurking.
In a mere thirty seconds, its forces set free
It's all broken up—and it's working.

WIGRAINE®

Truly fast-acting because of rapid disintegration, Wigraine tablets each contain 1.0 mg ergotamine tartrate and 100.0 mg caffeine to abort head pain; 0.1 mg belladonna alkaloids to alleviate nausea and vomiting; and 130.0 mg acetophenetidin to relieve residual occipital muscle pain. Available foil-stripped for easy carrying in boxes of 20.



Organon INC.
ORANGE, N. J.

Depropanex®

DEPROTEINATED PANCREATIC EXTRACT

promptly relieves smooth muscle spasm

MAJOR ADVANTAGES: Physiologic relief of pain. Non-narcotic. Non-toxic.

You can relieve spasm in 3 minutes with DEPROPANEX[1]

DEPROPANEX, by relieving smooth muscle spasm, is valuable in ureteral, renal and biliary colic and in various urologic instrumental procedures.

Intermittent claudication is markedly improved with DEPROPANEX.[2,3] DEPROPANEX also helps control post-operative paralytic ileus.

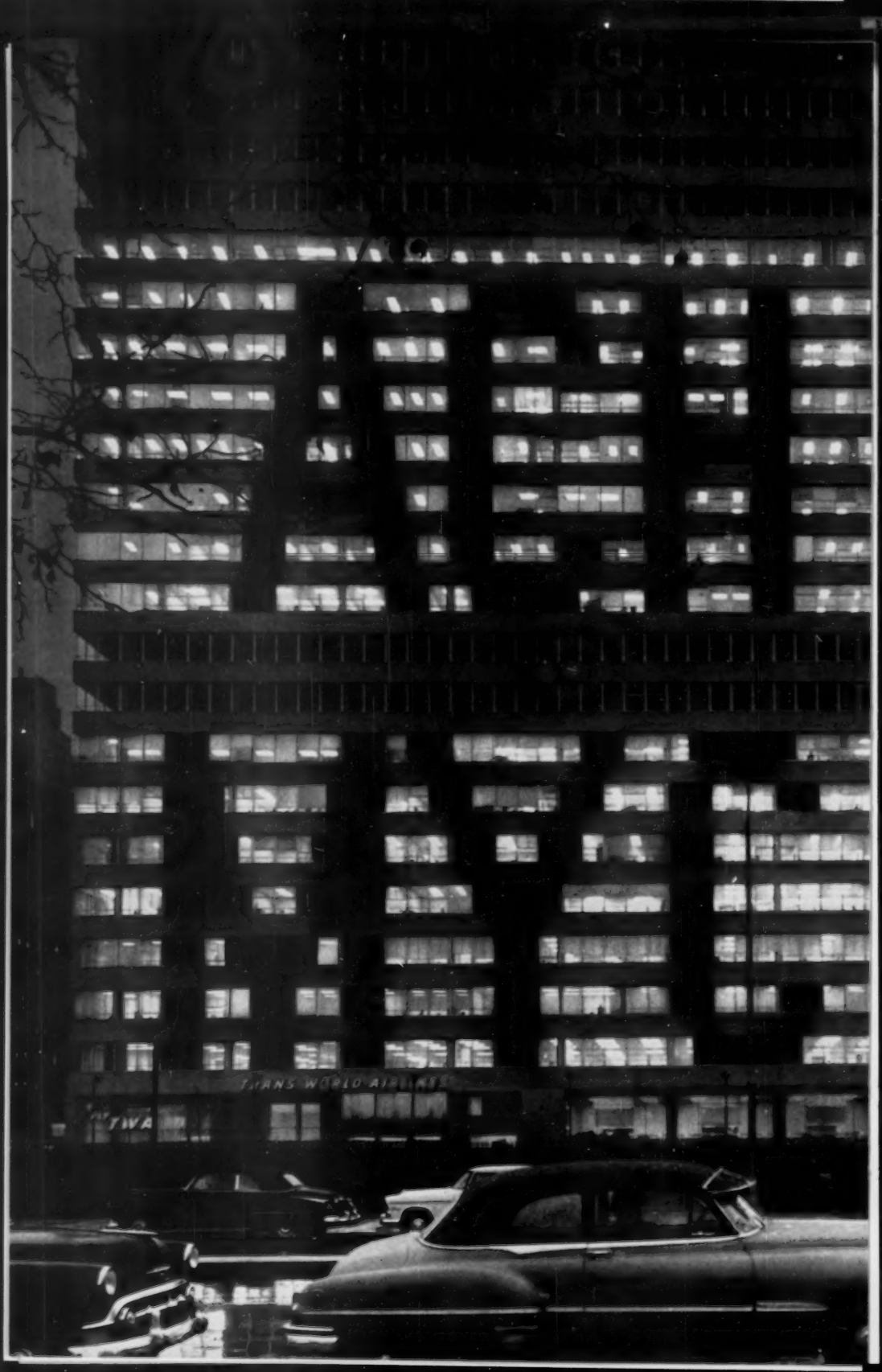
That DEPROPANEX has "beneficial effect . . . throughout the post-operative period has been convincingly demonstrated."[4] There is less nausea, little need for intravenous fluids, for nasal suction or enemas.[4]

Dosage: 2 to 5 cc. *Supplied* in 10 and 30 cc. rubber-capped vials.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

References: 1. South. M. J. 31:233 (March) 1938. 2. Bull. New York Acad. Med. 19:478, (July) 1943. 3. Am. Heart J. 18:425 (Oct.) 1939. 4. Minnesota Med. 33:1102 (Nov.) 1950.


TRANS WORLD AIRLINES
TWA

ACHROMYCIN*

Tetracycline *Lederle*

In the treatment of

respiratory infections

January and his associates[1] have written on the use of tetracycline (ACHROMYCIN) to treat 118 patients having various infections, most of them respiratory, including acute pharyngitis and tonsillitis, otitis media, sinusitis, acute and chronic bronchitis, asthmatic bronchitis, bronchiectasis, bronchial pneumonia, and lobar pneumonia. Response was judged good or satisfactory in more than 84% of the total cases.

Each month there are more and more reports like this in the literature, documenting the great worth and versatility of ACHROMYCIN. This antibiotic is unsurpassed in range of effectiveness. It provides rapid penetration, prompt control. Side effects, if any, are usually negligible.

No matter what your field or specialty, ACHROMYCIN can be of service to you. For your convenience and the patient's comfort, Lederle offers a *full* line of dosage forms, including

ACHROMYCIN SF

ACHROMYCIN with STRESS FORMULA VITAMINS. Attacks the infection—defends the patient—hastens normal recovery. For severe or prolonged illness. Stress formula as suggested by the National Research Council. Offered in Capsules of 250 mg. and in an Oral Suspension, 125 mg. per 5 cc. teaspoonful.

For more rapid and complete absorption. Offered only by Lederle!

[1]January, H. L. et al: Clinical experience with tetracycline. *Antibiotics Annual* 1954-55, p. 625.

Lederle

LEDERLE LABORATORIES DIVISION
AMERICAN CYANAMID COMPANY
PEARL RIVER, NEW YORK

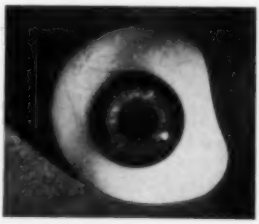
*REG. U.S. PAT. OFF.

PHOTO DATA: 4X5 VIEW CAMERA, F5.6, 1/25 SEC., EXISTING LIGHTING AT DUSK, ROYAL PAN FILM.

EVERY WOMAN
WHO SUFFERS
IN THE
MENOPAUSE
DESERVES
"PREMARIN"

widely used
natural, oral
estrogen

AYERST LABORATORIES
New York, N. Y. • Montreal, Canada
5646



SATISFACTION GUARANTEED

Specialists in Plastic and Glass Artificial Human Eyes Exclusively

Referred Cases Carefully Attended

FRIED & KOHLER, Inc.
665 FIFTH AVENUE near 53rd Street
NEW YORK, N. Y. Tel. ELdorado 5-1970

PROTEIN-BOUND IODINE
TOTAL IODINE
PAPER ELECTROPHORESIS
CATECHOL-AMINES
STEROID CHEMISTRY
CLINICAL CHEMISTRY

BOSTON MEDICAL LABORATORY

Directors
JOSEPH BENOTTI NORBERT BENOTTI
Medical Director
FRANCESCA M. RACIOPPI
19 Bay State Road
Boston 15, Mass.
KEnmore 6-0348 — 0533
PROMPT SERVICE

MONODRAL® with MEBARAL®

for peptic ulcer • gastro-intestinal tension and irritability

An exclusive combination designed to relieve pain, reduce tension and promote healing through effective inhibitory central and vagal-parasympathetic actions influencing all known etiologic factors in peptic ulcer.

anticholinergic • sedative

with unusually high antisecretory action • dependable antispasmodic effect • no drowsiness

Isolates the Ulcer

Each tablet contains:

MONODRAL* bromide	5 mg.
MEBARAL**	32 mg.

Dosage: 1 or 2 tablets three or four times daily. ***Available*** on prescription only. Bottles of 100 tablets.

Winthrop LABORATORIES

New York 18, N.Y. • Windsor, Ont.

*Controls hyperacidity and hypermotility

**Sedates without drowsiness

Monodral (brand of penthienate) and Mebaral (brand of mephobarbital), trademarks reg. U.S. Pat. Off.

Mallinckrodt®

barium sulfate USP

CHARLES B. TOWNS HOSPITAL *Established 1901*

FOR THE TREATMENT OF ALCOHOLISM

NARCOTIC AND BARBITURATE

ADDICTIONS EXCLUSIVELY

Complete Treatment at predetermined cost. Privacy of patient is assured—if desired.

Literature on Request

Edward B. Towns, *Director*

293 Central Park West, N. Y. 24, N. Y.
SChuyler 4-0770

Member American Hospital Association

THIASTIGMINE®

EFFECTIVE THERAPY FOR PROMPT RELIEF IN THE TREATMENT OF

NEURITIS NEURALGIAS HERPES ZOSTER

For Intramuscular Use

CONTAINS

Thiamine Hydrochloride—0.100 Atropine Sulfate—0.0002
Neostigmine Methylsulfate—0.0005
in a Stabilized Aqueous solution

SUPPLIED

KIRK No. 339 10 cc. multiple dose rubber capped vial.
KIRK No. 347 1 cc. ampul in boxes of 12 and 25.

C. F. KIRK LABORATORIES, NEW YORK 11, U. S. A.

Reprints available — Dept. TH

The
NEW
Phenothiazine
Derivative

Sparine*

Promazine Hydrochloride
10-(3-dimethylamino-n-propyl)-phenothiazine hydrochloride

For the Management of the Acutely Agitated Patient

• ***The acute alcoholic*** • ***The acute psychotic*** • ***The drug addict***

A promising new agent in chemopsychotherapeutics, **SPARINE** has demonstrated impressive effectiveness in controlling acute excitation without inducing significant side-reactions.[1,2,3]

SPARINE is a new, clinically effective phenothiazine derivative, which may be administered intravenously, intramuscularly, or orally. The route and dosage are determined by the extent of central-nervous-system excitation and by the patient's response.

Supplied: Tablets, 25, 50, and 100 mg., bottles of 50 and 500; 200 mg., bottles of 500. Injection, 50 mg. per cc., vials of 2 and 10 cc.

Wyeth®
Philadelphia 1, Pa.

1. Seifter, J., et al.: To be published. 2. Fazekas, J.F., et al.: M. Ann. District of Columbia 25:67 (Feb.) 1956. 3. Mitchell, E.H.: J.A.M.A. In press.

*Trademark

An Exclusive Development of Wyeth Research

Thirst, too, seeks quality

Coca-Cola
makes any pause
the pause
that refreshes

Upjohn

Bacterial diarrheas . . .

Kaopectate

Trademark, Reg. U.S. Pat. Off.

with Neomycin

Each fluidounce contains:

Neomycin sulfate . 300 mg. (4⅗ grs.)
[equivalent to 210 mg. (3¼ grs.) neomycin base]
Kaolin . . . . . 5.832 Gm. (90 grs.)
Pectin . . . . . 0.130 Gm. (2 grs.)
Suspended with methylcellulose 1.25%

Supplied:

6-fluidounce and pint bottles

The Upjohn Company, Kalamazoo, Michigan

Herald Square, N. Y.

Parkchester, Bronx *Jamaica, Queens*

White Plains, N. Y. *Flatbush, Brooklyn*

MACY'S PRESCRIPTION DEPARTMENT

Macy's is up-to-the-minute. We make every effort to have all new or scarce drugs on hand for your prescription. We follow the development of each new product, obtain it as soon as it is available. And when you prescribe, you can be assured that your prescription is accurately compounded exactly as you write it, carefully checked by our supervising pharmacists.

No wonder so many physicians prefer Macy's Prescription Department.

"It makes sense...

Veratrite is a good prescription in hypertension."

Physicians depend upon Veratrite in treating hypertension because—through the years—this combination has produced gratifying results in the widest range of patients.

Veratrite contains cryptenamine—a newly isolated alkaloid fraction that dependably lowers blood pressure without serious side effects. The formulation combines central-acting and local-acting agents to combat vasospasm.

Each Veratrite tabule supplies:

Cryptenamine (as tannate salt)	40 C.S.R.* Units
Sodium Nitrite	1 gr.
Phenobarbital	¼ gr.

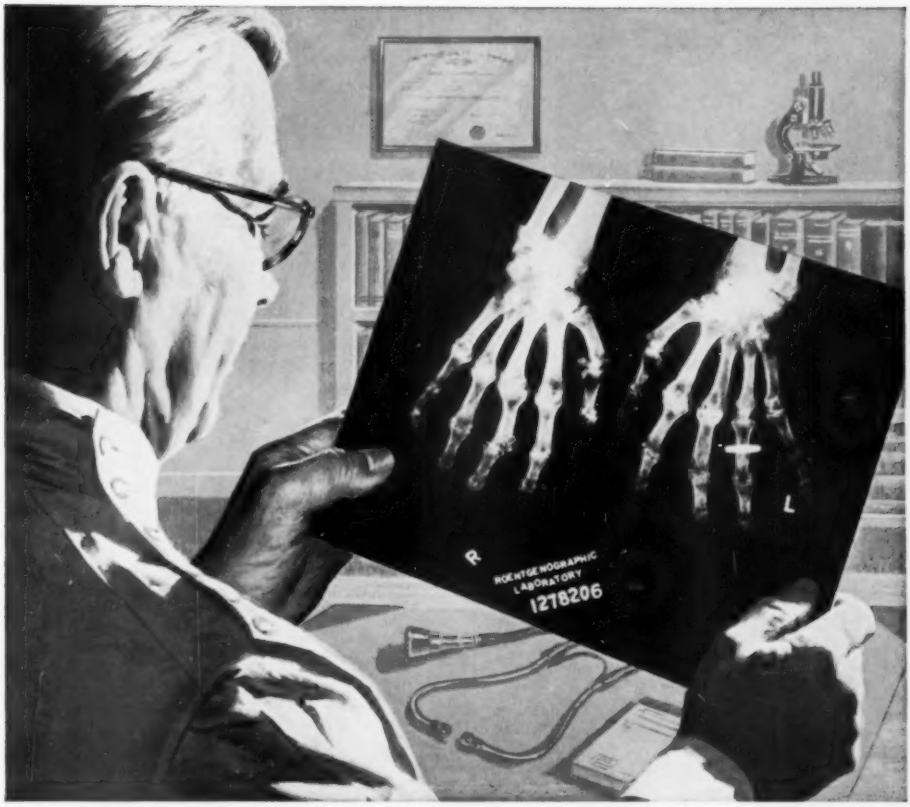
*Carotid Sinus Reflex

Bottles of 100, 500 and 1000 tabules

You will find that Veratrite saves the patient ½ the cost of medication in long-term management of hypertension. In fact, the most economical prescription you can write is

Veratrite®

IRWIN, NEISLER & COMPANY
DECATUR, ILLINOIS



Personalize Arthritis Therapy with Steroids plus BUFFERIN®

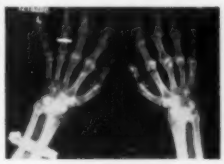
Exploit fully the use of salicylates in arthritis—give steroids in minimal doses—combine salicylates with corticosteroids for additive antiarthritic effect—this is the program Spies[1] advocates in a recent article in the Journal of the American Medical Association.

Treatment of rheumatoid arthritis demands a "highly individualized program," Spies[1] writes. The additive action of salicylates permits use of smaller amounts of hormones, thus lessening or eliminating their well-known side effects. "A proper mixture of salicylates and corticosteroids produces an effective antirheumatic agent in many cases."[1]

Suit your treatment to your individual arthritic patient. Use the hormone you prefer, in the dosage you think best, but for better results combine it with BUFFERIN, the salicylate proved to be better tolerated by arthritics.[2]

BUFFERIN contains no sodium, a marked advantage when cardiorenal complications make a salt-restricted diet necessary.

Each BUFFERIN tablet contains 5 grains of acetylsalicylic acid and the antacids magnesium carbonate and aluminum glycinate.



REFERENCES:
1. J.A.M.A. 159:645 (Oct. 15) 1955.
2. J.A.M.A. 158:386 (June 4) 1955.

BRISTOL-MYERS CO., 19 West 50 Street, New York 20, N. Y.

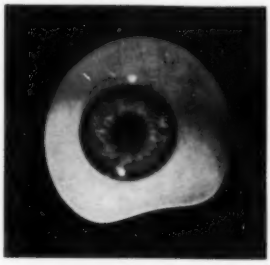
PATIENTS ON "MEDIATRIC" CAN EXPECT A HEALTHIER, HAPPIER "SECOND FORTY YEARS"

Steroid-Nutritional Therapy Provides a Constructive Approach in Preventive Geriatrics

"MEDIATRIC"®

AYERST LABORATORIES
New York, N.Y. • Montreal, Canada
5659

PLASTIC AND GLASS EYES



MAGER & GOUGELMAN, Inc.

OVER A CENTURY OF SERVICE • 1851-1956

- PRIVATE FITTINGS
- PERSONAL ATTENTION
- EXPERIENCE & SKILL

510 MADISON AVE., N. Y. 22
Telephone PLaza 5-3756

For acidosis due to anesthesia — edema

KALAK

Counter-Acts

ANTI-BIOTIC REACTIONS

. . . . KALAK is a non-laxative, alkaline diuretic buffer — side reactions from aureomycin — terramycin — sulfas — penicillin are reduced through the use of KALAK — KALAK contains only those salts *NORMALLY* present in plasma. . . . IT IS BASIC!

KALAK WATER CO.
of NEW YORK, Inc.
90 West St., New York 6, N. Y.

For acidosis due to nausea — in nephritis

Reduces Muscular Tension

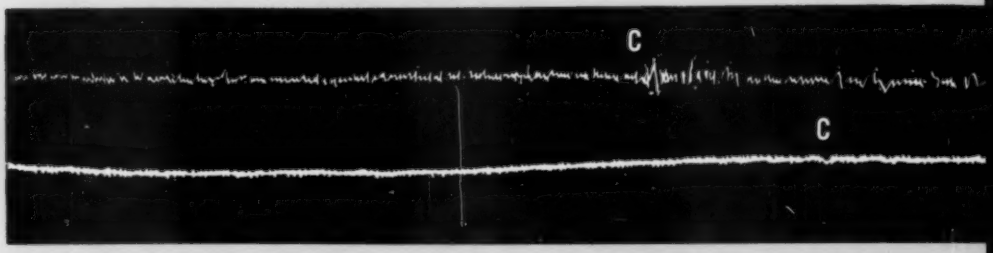
Equanil*

MEPROBAMATE

(2-methyl-2-n-propyl-1,3-propanediol dicarbamate)

Licensed under U.S. Patent No. 2,724,720

Electromyography shows decisive response



Electromyographic study of neuromuscular hyperactivity in 42-year-old male with anxiety-tension syndrome. A, Before EQUANIL; action potential of high amplitude and frequency. B, After one week of ambulatory treatment with EQUANIL; showing definite reduction in tension, greater ability to relax, and marked improvement in muscular coordination. C, Point where patient makes effort to relax.[1]

The remarkable effectiveness of EQUANIL may be demonstrated in two ways. One is by its ability to relieve muscle spasm and neuromuscular tension.[1] The second is by its ability to relieve mental tension and anxiety.

Usual dosage: 1 tablet t.i.d. The dose may be adjusted either up or down, according to the clinical response of the patient.

Supplied: Tablets, 400 mg., bottles of 50.

1. Dickel, H.A., et al.: West. J. Surg., April, 1956.

anti-anxiety factor with muscle-relaxing action . . . relieves tension

Wyeth®

Philadelphia 1, Pa.

*Trademark

Lift the depressed patient up to normal without fear of overstimulation . . .

with new

Ritalin®

A HAPPY MEDIUM IN PSYCHOMOTOR STIMULATION

• *Boosts the spirits, relieves physical fatigue and mental depression . . . yet has no appreciable effect on blood pressure, pulse rate or appetite.*

Ritalin is a mild, safer central-nervous-system stimulant which gently improves mood, relieves psychogenic fatigue "without let-down or jitters . . ."[1] and counteracts oversedation caused by barbiturates, chlorpromazine, rauwolfia, and antihistamines.

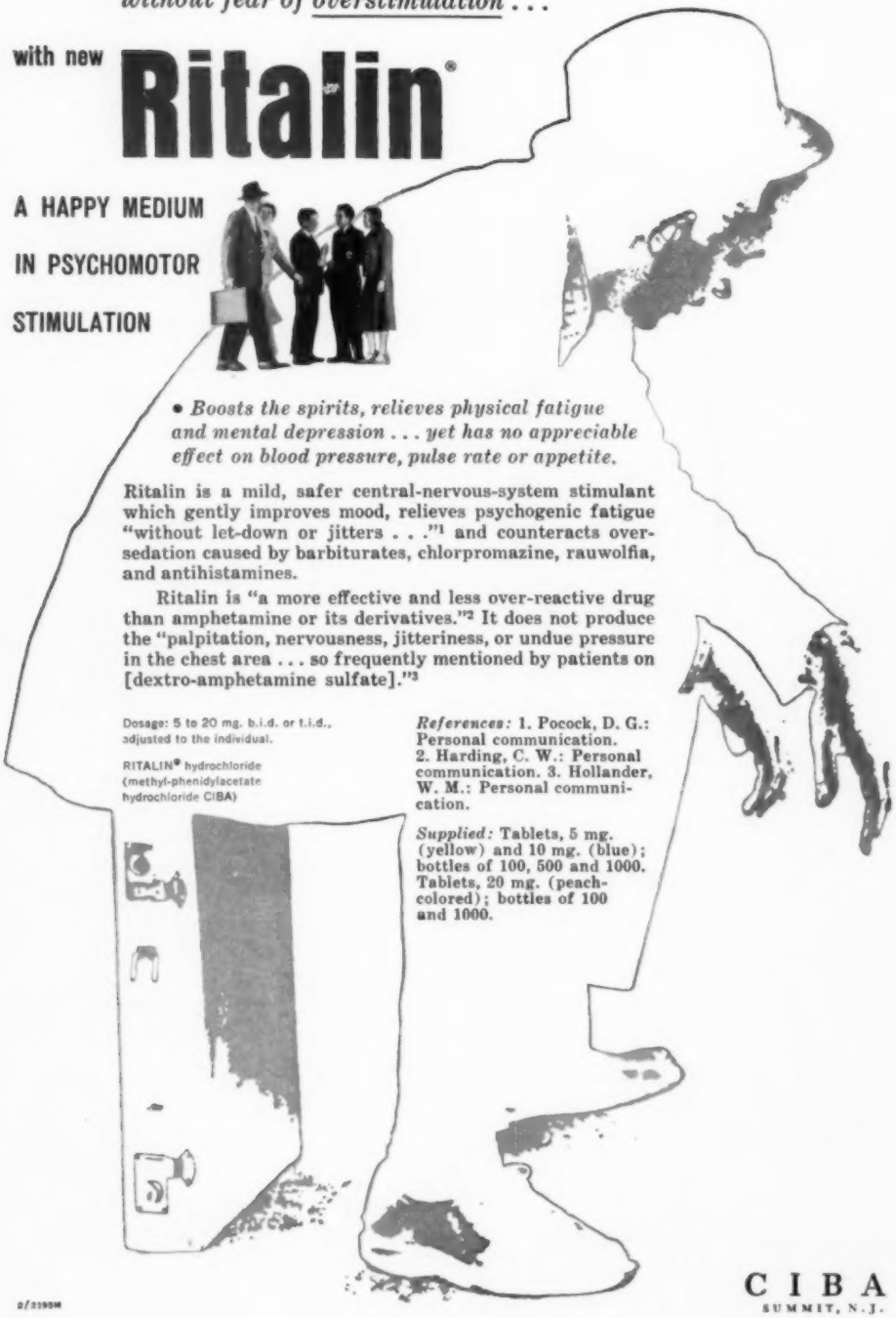
Ritalin is "a more effective and less over-reactive drug than amphetamine or its derivatives."[2] It does not produce the "palpitation, nervousness, jitteriness, or undue pressure in the chest area . . . so frequently mentioned by patients on [dextro-amphetamine sulfate]."[3]

Dosage: 5 to 20 mg. b.i.d. or t.i.d., adjusted to the individual.

RITALIN® hydrochloride (methyl-phenidylacetate hydrochloride CIBA)

References: 1. Pocock, D. G.: Personal communication. 2. Harding, C. W.: Personal communication. 3. Hollander, W. M.: Personal communication.

Supplied: Tablets, 5 mg. (yellow) and 10 mg. (blue); bottles of 100, 500 and 1000. Tablets, 20 mg. (peach-colored); bottles of 100 and 1000.



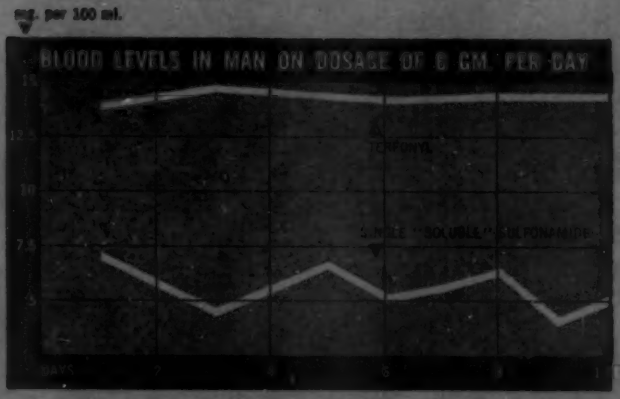
CIBA
SUMMIT, N.J.

9/21904M

maximum efficacy with minimum risk

Terfonyl

SQUIBB METH-DIA-MER SULFONAMIDES



Terfonyl is absorbed as well as single "soluble" sulfonamides, but is eliminated at a slower rate. For this reason, Terfonyl blood levels are much higher.

In experimental infections (Klebsiella, Pneumococcus, Streptococcus), Meth-Dia-Mer sulfonamides have been shown to be from three to four times more effective on a weight basis than single "soluble" sulfonamides.

Toxicity is minimal because normal dosage provides only one-third the normal amount of each sulfonamide. The body handles each component as though it were present alone, although therapeutic effects are additive.

Terfonyl Tablets, 0.5 Gm., bottles of 100 and 1000.
Terfonyl Suspension, 0.5 Gm. per 5 ml., pint bottles.

0.167 Gm. each of sulfamethazine, sulfadiazine and sulfamerazine per tablet or per 5 ml. teaspoonful of suspension.

SQUIBB

"TERFONYL"® IS A SQUIBB TRADEMARK

Just Published—Stevenson

MENTAL HEALTH PLANNING for SOCIAL ACTION

By GEORGE S. STEVENSON, M.D., Sc.D. National and International Consultant, The National Association for Mental Health, Inc. Consultant, U.S. Public Health Service, Department of Health, Education and Welfare, National Institute of Mental Health, and Veterans Administration.

"There is more scientific knowledge and technique for dealing with mental illness than is now being used." This is the challenge Dr. Stevenson presents. How we can use our current knowledge to a fuller extent and toward better results is set forth in this thorough and wide-ranging book. CONTENTS: PART I—Basic Considerations. 1. Introduction—Meaning, Range, History, and Agencies 2. Program Planning PART II—The Restoration of Mental Health. 3. The Mentally Disordered 4. State and Local Psychiatric Services 5. Veterans' Psychiatric Services 6. Private Psychiatry 7. The U.S. Public Health Service and Narcotic Addiction 8. Psychiatry in the General Hospital and General Medical Practice 9. Provisions for the Mentally Deficient 10. The Legal Offender, The Police, and the Court 11. The County Home and Mental Health of the Aged 12. The Halfway House 13. Outpatient Services and Residential Care of Mentally Ill Children 14. Nonpsychiatric Agencies Serving the Deviant PART III—The Protection of Mental Health. 15. Public Health and the Prevention of Mental Disorder PART IV—Elevation of Mental Health. 16. Positive Mental Health 17. The Home and Family 18. Mental Health and the Church 19. Mental Hygiene and the School 20. Military Defense Services 21. Mental Health and Work 22. Mental Health and Recreation PART V—Special Considerations. 23. Program Execution and Social Action 24. World Mental Health—Visual Aids—Index. 318 pages, 6 x 9.....$5.50

New—Speert and Guttmacher

OBSTETRIC PRACTICE

By HAROLD SPEERT, M.D., Associate in Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons; Assistant Attending Obstetrician and Gynecologist, Presbyterian Hospital and ALAN F. GUTTMACHER, M.D., Director of Obstetrics and Gynecology, the Mount Sinai Hospital; Clinical Professor of Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons.

This, the fourth volume in the Series of Handbooks for the General Practitioner is specifically designed to meet the needs of the doctor in general practice who provides obstetrical care to the expectant mothers in his community. The authors clearly state the value and purpose of OBSTETRIC PRACTICE in their introduction: "Our aim has been to make this a practical up-to-date guide to assist the physician in the actual care of his obstetrical patients."

CONTENTS: Changes in the Maternal Organism. The Diagnosis of Pregnancy. Other Obstetrics—Antepartum Care. The Obstetric Pelvis. Pregnancy Hygiene. Minor Complaints of Pregnancy. Spontaneous Abortion and Fetal Death in Utero. Ectopic Pregnancy. Hydatidiform Mole and Chorioncarcinoma. Other Conditions Causing Vaginal Bleeding in Early Pregnancy. Infections in Pregnancy. Cardiovascular Diseases in Pregnancy. Metabolic Disorders in Pregnancy. Blood Dyscrasias in Pregnancy. Neurological Disorders in Pregnancy. Diseases of the Urinary Organs in Pregnancy. Surgical Complications of Pregnancy. Gynecological Complications of Pregnancy. Therapeutic Abortion. Growth and Orientation of the Fetus. Multiple Pregnancy. Toxemia of Pregnancy. Bleeding Complications of Late Pregnancy. The Onset of Labor, Normal Labor and Delivery. Problems in Labor. Operative Obstetrics. Obstetrical Analgesia and Anesthesia. The Normal Puerperium and Lactation. Postpartum and Puerperal Hemorrhage. Puerperal Infection. Other Complications of the Puerperium. The Newborn. The Post-Puerperal Survey. 459 pages, 5½ x 8½. $7.00.

BLAKISTON DIVISION, McGRAW-HILL BOOK COMPANY, INC.

330 WEST 42nd STREET, NEW YORK 36, NEW YORK